QUTENZA® (CAPSAICIN 8% PATCH) FOR THE MANAGEMENT OF NEUROPATHIC PAIN ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS-ASSOCIATED PERIPHERAL NEUROPATHY

BRIEFING DOCUMENT FOR THE ANESTHESIA AND ANALGESIA DRUG PRODUCTS ADVISORY COMMITTEE MEETING

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BOCF	Baseline Observation Carried Forward
BP	Blood Pressure
BPI	Brief Pain Inventory Short Form
bpm	Beats per Minute
BUN	Blood Urea Nitrogen
CART	Combination Anti-retroviral Therapy
aCD4	Cluster of Differentiation Antigen 4
CGIC	Clinical Global Impression of Change
CI	Confidence Interval
cm	Centimeter
cm^2	Centimeter Squared
C_{max}	Maximum Concentration
DB	Double-blind
DSP	Distal Symmetrical Polyneuropathy
ECG	Electrocardiogram
EMA	European Medicines Agency
ENFD	Epidermal Nerve Fiber Density
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type 1
HIV-PN	Human Immunodeficiency Virus-Associated Peripheral Neuropathy
HR	Heart Rate
IND	Investigational New Drug
ITT	Intent-to-Treat
kg	Kilogram
L	Liter
LLOQ	Lower Limit of Quantitation
LMX4®	Lidocaine 4%
LOCF	Last Observation Carried Forward
LS Mean	Least Squares Mean
M1	16-hydroxy-capsaicin

Abbreviation	Definition
M2	16,17-dehydro-capsaicin
M3	17-hydroxy-capsaicin
m^2	Meter Squared
µmol	Micromole
mg	Milligram
min	Minutes
mL	Milliliter
mm	Millimeters
mmHg	Millimeters Mercury
mmol	Millimole
ng	Nanogram
NGX-4010	Capsaicin 8% patch, Qutenza®
nM	Nanomolar
NPRS	Numeric Pain Rating Scale
NS	Not Significant
PC	Placebo-Controlled
PDN	Painful Diabetic Neuropathy
PGIC	Patient Global Impression of Change
PGP	Protein Gene Product (9.5 Immunostaining)
PHN	Postherpetic Neuralgia
PPI	Present Pain Intensity
p.r.n.	Pro Re Nata (not scheduled as in drug dosing; drug taken as needed)
QST	Quantitative Sensory Testing
R	Randomized
rhNGF	Recombinant Human Nerve Growth Factor
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAT	Self-Assessment of Treatment
SD	Standard Deviation
SE	Standard Error
SF-36v2™	SF-36v2™ Health Survey
SFMPQ	Short-Form McGill Pain Questionnaire
SSRI	Serotonin Selective Reuptake Inhibitor
TRPV1	Transient Receptor Potential Vanilloid 1
US	United States
WBC	White Blood Count

Abbreviation	Definition
w/w	Weight to Weight

EXECUTIVE SUMMARY

Neuropathic pain is defined currently as "pain caused by a lesion or disease of the somatosensory system" [Jensen 2011]. Hyperactive cutaneous nociceptors located in the skin are believed to be an important pathophysiological mechanism contributing to the generation of pain in many peripheral neuropathic syndromes including postherpetic neuralgia (PHN) and human immunodeficiency virus (HIV)-associated peripheral neuropathy (HIV-PN) [Campbell 2006; Anand 2011].

The Capsaicin 8% Patch (marketed as Qutenza® (capsaicin) 8% dermal patch; previously designated NGX-4010) was approved by the FDA for the management of neuropathic pain associated with PHN in November 2009. Capsaicin received an orphan drug designation from the FDA in 2003 for the treatment of pain associated with HIV-PN. On 6 September 2011, NeurogesX submitted a supplemental application to FDA seeking approval for use of the Capsaicin 8% Patch for the management of neuropathic pain associated with HIV-PN.

HIV-PN is the most common neurological complication of HIV infection and a major cause of morbidity [Evans 2011]. The pathogenesis of HIV-PN is likely to be multifactorial as it can be caused by HIV-associated immune- and viral protein-mediated neurotoxicity and inflammation, by therapy with neurotoxic anti-retroviral medications, and/or by agents used for the treatment of opportunistic infections or neoplasias [Wallace 2009; Bhangoo 2009]. Risk factors for HIV-PN include advancing age, lower CD4 (cluster of differentiation antigen 4) nadir, current use of combination anti-retroviral therapy, and past use of dideoxynucleoside analogues. Despite the widespread use of effective combination anti-retroviral therapy (CART), Ellis and colleagues found that over half of HIV patients have signs of HIV sensory neuropathy and nearly 40% of these patients report peripheral neuropathic pain [Ellis 2010].

At present, there are no FDA-approved or standard-of-care therapies for the management of neuropathic pain associated with HIV-PN. In general, studies of medications used to treat pain in subjects with HIV-PN have yielded generally disappointing results. A recent systematic review of randomized, controlled studies concluded that evidence of efficacy in the treatment of neuropathic pain associated with HIV-PN exists only for the Capsaicin 8% Patch, smoked cannabis, and subcutaneous recombinant human nerve growth factor (rhNGF) [Phillips 2010].

Summary of the Capsaicin 8% Patch Approved Labeling in PHN

The Capsaicin 8% Patch has been developed to deliver a therapeutic dose of capsaicin to the epidermis, the presumed location of hyperactive nociceptors in patients with peripheral neuropathic pain. Physicians or health care professionals apply up to four Capsaicin 8% Patches to the most painful skin areas (typically on the trunk in a dermatomal pattern) in patients with PHN for 60 minutes. Treatment can be repeated every three months or more as indicated by the return of pain. The most common adverse reactions (≥5% and greater than control) are application site erythema, application site pain, application site pruritus and application site papules. In clinical trials, increases in blood pressure occurred during or shortly after exposure to the Capsaicin 8% Patch (the changes averaged less than 10 mm Hg). The observed increases in blood pressure were unrelated to baseline blood pressures but were associated with changes in treatment-related pain.

Pharmacodynamics and Pharmacokinetic Summary

Capsaicin is an agonist for the transient receptor potential vanilloid 1 (TRPV1) ion channel-receptor complex expressed on nociceptive nerve fibers in the epidermis. Topical administration of capsaicin directly stimulates TRPV1-expressing epidermal nociceptors, and may lead to the sensation of local burning and/or pricking pain with an accompanying erythema that occurs during, and, in most subjects, for approximately an hour following topical capsaicin application.

Over the subsequent period of several days, there is a gradual decrease in baseline pain symptoms in many subjects that is believed to be mediated by a reduction in the number and/or function of TRPV1-expressing nociceptors in the epidermis. In clinical pharmacodynamics studies, reduced epidermal nerve fiber density (ENFD) and minor changes in cutaneous nociceptive function (i.e., thermal detection and sharp sensation) were noted one week after exposure to the Capsaicin 8% Patch. However, these effects were fully reversible over the course of several months. During this time period, there may be a gradual return of neuropathic pain symptoms that is theoretically mediated by a re-innervation of the treated area by TRPV1-expressing hyperactive nociceptors.

Systemic exposure to capsaicin following a 60-minute application of the Capsaicin 8% Patch is limited. Pharmacokinetic data in HIV-PN subjects showed no quantifiable systemic exposure above the detection threshold of 0.5 ng/mL. Following treatment with the Capsaicin 8% Patch for 90 minutes, limited systemic exposure was observed in 3 of 37 HIV-PN subjects (8%). The

highest capsaicin plasma level (C_{max}) observed after a 90-minute patch application was 1.75 ng/mL and was observed around the time of Capsaicin 8% Patch removal from the skin. Capsaicin plasma levels decreased to below the limit of detection 3 hours after Capsaicin 8% Patch removal in all 3 of these HIV-PN subjects.

Overview of Studies C107 and C119

Evidence for the efficacy of the Capsaicin 8% Patch in the treatment of pain associated with HIV-PN is based on the results of 2 Phase 3, multicenter, randomized double-blind, controlled studies: pivotal Study C107 and Study C119. Eligible subjects were adults (≥18 years) with HIV-1 infection who had moderate to severe neuropathic pain in both feet secondary to HIV-PN resulting from HIV-1 disease and/or anti-retroviral drug exposure. Subjects were allowed to remain on stable chronic analgesic medication regimens during the studies, but were not allowed to use any topical analgesic medications on the affected areas. Subjects could receive concomitant medications including opioids if administered orally or transdermally at a total daily dose not exceeding morphine 60 mg in Study C107 and 80 mg in Study C119, or its equivalent.

Subjects received a single, randomized treatment and were then followed over a 12-week double-blind period. Prior to placement of study patches, subjects received pre-treatment with a topical local anesthetic (lidocaine 4% cream) applied on their painful areas for 60 minutes. After removal of the topical anesthetic, randomized treatment was applied over the painful areas, which was a single application of low-dose Control (containing 0.04% capsaicin) patch (hereafter referred to as low-dose Control) or Capsaicin 8% Patch for 30, 60, or 90 minutes in Study C107 and 30 or 60 minutes in Study C119. After completion of the assigned treatment time, the patches were removed and the treatment areas were cleansed using a study-supplied cleansing gel. Subjects were monitored for at least 1-2 hours following treatment before being discharged and were asked to return for follow-up visits.

The primary efficacy measure for studies C107 and C119 was the percent change in mean Numeric Pain Rating Scale (NPRS) scores from Baseline to Weeks 2 to 12. The NPRS is an 11-point scale (0 to 10), with 0 indicating no pain and 10 indicating worst possible pain [Farrar 2001]. Subjects used this scale each evening to rate the “average pain for the past 24 hours” for their painful area(s). No further exposure to the Capsaicin 8% Patch occurred during the 12-week evaluation period. The NPRS scores from Week 1 were not analyzed in the primary endpoint analysis in order to avoid the potential confounding bias due to the protocol-allowed use of add-on analgesic medications for treatment-related discomfort during Week 1.

Efficacy Findings

The primary endpoint of HIV-PN pivotal Study C107 showed that the pooled Capsaicin 8% Patch treatment groups demonstrated significantly greater pain reduction from Baseline to Weeks 2 to 12 compared to the pooled low-dose Control groups ($P < 0.003$). In addition, the Capsaicin 8% Patch 90-minute application time group demonstrated a statistically significant pain reduction from Baseline at Weeks 2 to 12 compared to the pooled low-dose Control groups ($P = 0.0046$).

Multiple prespecified secondary endpoints in Study C107 were statistically significantly better than the control arm with a nominal P value < 0.05. These secondary endpoints included the responder rate (i.e., $\geq$30% pain reduction from Baseline) during Weeks 2 to 12 and the Gracely Pain Score, Brief Pain Inventory Short Form (BPI), Short-Form McGill Pain Questionnaire (SFMPQ), Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), and Self-Assessment of Treatment (SAT) questionnaire at Week 12/Termination.

Nominally statistically significantly differences favoring the Capsaicin 8% Patch 30-minute treatment group versus the pooled low-dose Control group were also noted for pain reduction from Baseline to Weeks 2 to 12 ($P = 0.0007$). Analyses of the primary endpoint using methods that adjust for multiplicity without assuming a linear dose response (e.g., Bonferroni method or Hochberg procedure) showed evidence of efficacy for the 30-minute treatment group and established the robustness of the results.

Across the 3 Capsaicin 8% Patch application times evaluated in Study C107, longer durations of treatment did not result in greater efficacy. As an exploratory analysis, the treatment (Capsaicin 8% Patch versus low-dose Control) by patch duration (30, 60, and 90 minutes) interaction effect was not statistically significant with $P = 0.323$. This result supports the conclusion of homogeneity of the differences between the respective doses and their corresponding controls (i.e., there appeared to be a flat dose response in terms of patch application times).

In Study C107, retreatment with Capsaicin 8% Patch was evaluated in an open-label setting, with the magnitude of pain reduction over multiple treatments being similar to that measured after the initial Capsaicin 8% Patch treatment. The median time to first retreatment (subjects were not allowed to receive a retreatment until Week 12) for the total Capsaicin 8% Patch group was significantly longer compared with the total low-dose Control group (18 weeks versus 13 weeks; $P = 0.0022$).

In the second HIV-PN study (Study C119), the observed amount of pain reduction from Baseline to Weeks 2 to 12 for the pooled Capsaicin 8% Patch treatment was larger than the pooled low-dose Control groups (-30% versus - 25%; $P < 0.10$), but the degree of pain reduction did not meet the prespecified primary endpoint analysis statistical criteria of significance (i.e., $P < 0.05$). Exploratory analyses showed that a single 30-minute Capsaicin 8% Patch treatment resulted in numerically greater pain reductions (-26% versus -19%) from Baseline to Weeks 2 to 12 compared to low-dose Control and was associated with nominally statistically significant improvements on the PGIC, CGIC, and SAT questionnaire. The exploratory nonparametric analyses showed a significant difference between the Total Capsaicin 8% Patch and the 30-minute Capsaicin 8% Patch groups and their respective Control groups.

Integrated analyses of these two HIV-PN Phase 3 studies showed that 30-minute Capsaicin 8% Patch treatments provided significantly more pain reduction from Baseline to Weeks 2 to 12 compared to low-dose Control, with consistent findings across subgroups (e.g., gender, age, race, Baseline pain score, duration of HIV-PN, use of neurotoxic antiretroviral, and use of concomitant neuropathic pain medications).

In addition, two key factors were identified that appear to have negatively impacted the efficacy signal. First, the results indicate that the observed efficacy signal may have been diluted by allowing up to 75% of the subjects in both studies to use concomitant analgesic medications. Second, given the greater variability observed in the C119 trial conducted across multiple geographic locations, use of nonparametric statistical tests would have been an alternative analysis approach to testing efficacy rather than the prespecified parametric tests used in the study.

Safety Findings

Safety data collected during the clinical development program in 1696 subjects who received Capsaicin 8% Patch (685 subjects with HIV-PN) support the conclusion that the Capsaicin 8% Patch is safe and well tolerated in subjects with HIV-PN and PHN.

Overall, a similar proportion of subjects (92% each) in the Capsaicin 8% Patch (all doses combined) and low-dose Control groups completed their participation in controlled HIV-PN studies (C107, C112, and C119). Early terminations due to adverse events (AEs) in these controlled studies occurred in 3 Capsaicin 8% Patch subjects (0.5%) and 2 low-dose Control subjects (0.8%). As expected following application of the Capsaicin 8% Patch, the

overwhelming majority of AEs in subjects with HIV-PN were local application site reactions. Specifically, the most frequently reported treatment-emergent AEs across all study groups were application site pain and erythema. Application site reactions were transient and, on average, decreased to near baseline levels within a few hours and resolved completely within 2 to 5 days. Analyses did not suggest any consistent relationship between incidence of application site events and treatment area or treatment duration.

A similar proportion (6% each) of subjects in the Capsaicin 8% Patch and low-dose Control groups experienced 1 or more serious adverse events (SAEs) in the controlled studies. All SAEs reported in the 3 controlled HIV-PN studies (C107, C112, and C119) during the 12-week blinded phase were considered to be of remote or no relationship to study medication.

Throughout the entire clinical development program, 9 subjects (7 HIV-PN and 2 PHN) died during their participation in a Capsaicin 8% Patch study. None of the deaths were considered clinically unusual or unexpected given the subjects' underlying disease and none of these deaths were considered by Investigators to be related to study medication.

Dermal assessment scores were higher in the Capsaicin 8% Patch group overall. Dermal assessment scores tended to increase with longer treatment durations but not with increasing number of treatments and these scores returned to Baseline levels within hours, on average, after patch removal. Overall, treatment-associated dermal irritation tended to be mild and transient.

In summary, the safety data collected in this clinical development program provide significant evidence of safety and support the use of the Capsaicin 8% Patch for 30-90 minutes in the management of painful HIV-PN without serious risk.

Benefit/Risk

The treatment of neuropathic pain associated with HIV-PN represents a major unmet medical need. At present, there are no approved therapeutic options for individuals suffering from pain and other related neuropathic symptoms associated with HIV-PN, which can have a significant negative impact on their quality of life.

The data from pivotal Study C107 provide robust statistical evidence (based upon the prespecified analysis plan) that treatment with the Capsaicin 8% Patch provides a clinically meaningful reduction of pain for up to 12 weeks after a single application in HIV-PN subjects, regardless of gender, age, race, Baseline pain score, concomitant neuropathic pain medication

use, HIV-PN duration, and neurotoxic antiretroviral use. These results were confirmed in the 90-minute application time cohort and were similar in the 30-minute application time cohort compared to the total Control cohort, based on exploratory statistical analyses. The clinical benefit of the Capsaicin 8% Patch treatment is also demonstrated by improvements in secondary endpoints associated with disease symptoms such as the Patient Global Impression of Change (PGIC) Score.

In Study C119, pain reduction during Weeks 2 to 12 was observed ($P < 0.10$) but it did not meet the prespecified statistical criteria of the primary endpoint (i.e., $P < 0.05$). However, Study C119 did provide evidence that subjects detected a clinical benefit of the treatment based on data derived from a number of secondary endpoints such as the PGIC, as well as in exploratory statistical analyses. The exploratory nonparametric analyses showed a significant difference between the Total Capsaicin 8% Patch and the 30-minute Capsaicin 8% Patch groups and their respective Control groups.

Therefore, the totality of the data from Studies C107 and C119 provides substantial evidence of clinical efficacy for the Capsaicin 8% Patch in the treatment of painful neuropathy associated with HIV-PN. This conclusion is supported by the prespecified primary endpoint analysis from Study C107, the prespecified secondary endpoint analyses from Studies C107 and C119, and the exploratory analyses of the integrated dataset.

In terms of safety, the Capsaicin 8% Patch treatment is well tolerated and it has not been associated with any clinically significant systemic, neurological, or sensory-related adverse effects. Adverse events are essentially limited to transient, small and clinically insignificant elevations in BP during treatment in association with treatment-related local pain and erythema at the patch application site. Repeated Capsaicin 8% Patch treatment is not associated with an increased incidence or severity of AEs. Furthermore, no new risks associated with the Capsaicin 8% Patch were identified in the HIV-PN studies compared to previous PHN studies or recent market surveillance data.

In summary, the totality of the clinical trial data provides substantial evidence of clinical efficacy with no serious safety concerns for the Capsaicin 8% Patch in the treatment of subjects with neuropathic pain associated with HIV-PN. Therefore, the clinical benefits of Capsaicin 8% Patch, in the absence of significant safety concerns, far outweigh its risks for patients suffering from painful HIV-PN who currently have no other approved therapeutic options for a clinical disorder that is both painful and can have a negative impact on their quality of life.

In conclusion, the data presented herein provide the rationale for FDA approval of Capsaicin 8% Patch for the treatment of pain associated with HIV-PN based on the following 3 main considerations:

1. HIV-PN is a major unmet medical need for which no approved therapeutics are available.

2. The totality of the data from the clinical development program for the Capsaicin 8% Patch has demonstrated substantial evidence of clinical efficacy in the treatment of pain associated with HIV-PN with a 30-minute dosing regimen. This effectiveness finding is also supported by the proven safety and efficacy of this therapy in individuals whose neuropathic pain is secondary to PHN, a related neuropathic pain condition that also appears to involve hypersensitive cutaneous nociceptors.

3. The clinical development program has demonstrated that Capsaicin 8% Patch has an excellent safety profile.

1. Introduction

The Capsaicin 8% Patch (Qutenza®; formerly designated NGX-4010) is a capsaicin 8% weight-to-weight (w/w) dermal patch (640 µg/cm^2) developed for the treatment of pain due to peripheral neuropathies. The Capsaicin 8% Patch was approved by the Food and Drug Administration (FDA) on 16 November 2009 for the management of neuropathic pain associated with postherpetic neuralgia (PHN) and by the European Medicines Agency (EMA) on 15 May 2009 for treatment of peripheral neuropathic pain in non-diabetic adults, either alone or in combination with other medicinal products for pain. These approvals were based on efficacy and safety data obtained from studies in subjects with PHN and painful human immunodeficiency virus (HIV)-associated peripheral neuropathy (HIV-PN).

According to its approved product label (Appendix A) in the United States (U.S.), only physicians or health care professionals under the close supervision of a physician can apply the Capsaicin 8% Patch (typically applied to the trunk area of subjects with PHN). Treatment can be repeated no more frequently than every three months, as warranted by the return of pain. In clinical studies supporting the PHN indication, adverse reactions occurring in ≥5% of subjects in the Capsaicin 8% Patch group and incidences greater than in the Control group were limited to application site events (i.e., pain, erythema, pruritus, and papules). Blood pressure was noted to increase (averaging <10 mm Hg in PHN subjects) during or shortly after exposure to Capsaicin 8% Patch; these changes lasted for approximately two hours after patch removal. Increases in blood pressure were related to treatment-related increases in pain, not to pretreatment blood pressure.

NeurogesX, Inc. (hereafter NeurogesX) is seeking approval to market the Capsaicin 8% Patch for the management of neuropathic pain associated with HIV-PN.

Background

Neuropathic pain is defined currently by the International Association for the Study of Pain as "pain caused by a lesion or disease of the somatosensory system" [Jensen 2011]. Neuropathic pain can originate in the peripheral nervous system or the central nervous system, although both systems may be involved in some conditions. Although peripheral neuropathic pain can arise from nerve injuries or diseases of various etiologies, hyperexcitable cutaneous nociceptors are thought to be an important pathophysiologic mechanism of pain generation in peripheral neuropathic pain syndromes including both HIV-PN and PHN [Campbell 2006; Anand 2011]. Clinical features of peripheral sensory neuropathy may include a variety of

disabling symptoms such as burning, stinging, shooting pain or electrical sensations, paresthesias, and sensitivity to light touch or noxious stimuli over the area (i.e., allodynia and hyperalgesia, respectively).

Although "pain" is the hallmark symptom, patients also complain of other symptoms that impact their quality of life such as discomfort when wearing socks and shoes, non-painful dysesthesia while moving sheets across their feet, sleep interruption, etc. An essential element in neuropathic pain is the combination of sensory loss and the paradoxical presentation of hypersensitivity in the painful area [Treede 2008; Harden 2003].

HIV-PN is the most common neurological complication of HIV infection and it is a major cause of morbidity, including adverse effects on physical and emotional functioning [Verma 2001; Ellis 2010]. Patients with HIV-PN predominantly report a distal sensory neuropathy that is characterized by symptoms in their feet, including paresthesias, pain, and numbness [Ellis 2010; Evans 2011]. The pathogenesis of HIV-PN is likely to be multifactorial, as it may be caused by HIV-associated immune- and viral protein-mediated neurotoxicity and inflammation, by therapy with neurotoxic anti-retroviral medications, or by agents used for the treatment of opportunistic infections or neoplasias [Wallace 2008; Bhangoo 2009]. A recent study found that over half of HIV patients evaluated had signs of HIV sensory neuropathy and nearly 40% of these patients reported neuropathic pain [Ellis 2010]. Neither race nor gender appears to be a risk factor for the development of HIV-PN [Evans 2011].

No medications have been approved by the FDA for the management of neuropathic pain associated with HIV-PN. To date, multiple medications used to treat neuropathic pain caused by other etiologies have yielded generally disappointing results in large randomized, controlled studies in subjects with HIV-PN (summarized in Appendix B) [Phillips 2010]. For example, although effective in some types of neuropathic pain, anticonvulsant agents have had inconsistent results in clinical trials of HIV-PN. A small placebo-controlled study found that gabapentin was more effective than placebo in reducing pain and sleep interference in subjects with HIV-PN [Hahn 2004]. A recent large, randomized, controlled study of pregabalin for the treatment of HIV neuropathy did not demonstrate it to be more effective than placebo [Simpson 2010]. No overall benefit was seen with lamotrigine [Simpson 2003]. Additional studies of tricyclic antidepressants have also failed to document evidence of effectiveness [Kieburtz 1998; Shlay 1998]. Similarly, Peptide T [Simpson 1996], mexiletine [Kemper 1998; Kieburtz 1998], acupuncture [Shlay 1998], lidocaine [Estanislao 2004], low-concentration

capsaicin (0.075%) [Paice 2000], and memantine [Schifitto 2006] were not effective in relieving pain from HIV-PN.

A few positive clinical trials have been reported for the treatment of pain associated with HIV-PN. For example, two small randomized, placebo-controlled studies in subjects with HIV-PN have shown that smoked cannabis reduced daily pain compared with placebo [Abrams 2007; Ellis 2009]. Treatment with subcutaneous recombinant human nerve growth factor (rhNGF) has also been reported to reduce pain in subjects with HIV-PN [McArthur 2000; Schifitto 2001]. Neither smoked cannabis nor rhNGF have been approved for clinical use in the treatment of pain associated with HIV-PN.

Thus, a substantial unmet medical need exists for the treatment of neuropathic pain associated with HIV-PN.

1.1 Regulatory History

The original NDA 22-395 for the Capsaicin 8% Patch was approved by the FDA on 16 November 2009 for the management of neuropathic pain associated with PHN. With the efficacy supplement NDA 22-395/013, NeurogesX is seeking approval of the Capsaicin 8% Patch for the management of neuropathic pain associated HIV-PN.

The terms HIV-associated neuropathy (HIV-AN) and HIV-PN have both been used in the literature to describe the same clinical condition. Documentation within the sNDA includes reference to the treatment of painful HIV-AN. However, recent market research by NeurogesX has indicated that the term HIV-AN may be confused with the terminology used to describe HIV-associated nephropathy. As HIV-AN and HIV-PN are synonymous terms for the same clinical condition, the term HIV-AN has been replaced with HIV-PN in this briefing document and sponsor presentation for this Advisory Committee meeting.

NeurogesX received FDA guidance from the Division of Anesthetic, Critical Care, and Addiction Drug Products (later named Division of Anesthesia, Analgesia and Rheumatology Products) during the development program for HIV-PN. The key development meetings and regulatory actions are listed below:

- Pre-Investigational New Drug (IND) Meeting – 26 June 2001: Discussed the development plan and the future IND submission for Capsaicin 8% Patch for the treatment of peripheral neuropathic pain.

- End-of-Phase 1 Meeting – 6 March 2003: Discussed the design of the well-controlled studies, including the selection of the efficacy endpoint and an appropriate control.

- FDA Office of Orphan Products Development Letter dated 2 May 2003 stated that capsaicin qualifies for orphan-drug designation for the treatment of painful HIV-PN.

- Type C Meeting Teleconference – 10 February 2004: Discussed the development plan for Capsaicin 8% Patch in HIV-PN, the size of safety database needed to support this program, and the statistical analysis plan intended to evaluate the HIV-PN and the PHN studies.

- Letter from Division dated 29 July 2004 stated that Capsaicin Dermal Patch for the treatment of painful HIV-associated neuropathy is designated as a fast-track product.

- End-of-Phase 2 Meeting (HIV-PN) – 26 October 2005: Discussed the adequacy of the painful HIV-associated neuropathy development program to support an NDA filing.

    - At the End-of-Phase 2 meeting in October 2005, data from Study C107, a randomized controlled study to evaluate efficacy of the Capsaicin 8% Patch in HIV-PN subjects, were submitted to the Agency. The Division noted that it was possible that Study C107 could be adequate to support efficacy but indicated that "a second adequate and well-controlled trial to further define efficacy and support your proposed dosing regimen" was "strongly encouraged" with similar design to Study C107. The Division commented that a second study would provide the opportunity to prospectively address the handling of multiple control groups.

    - Following the Division's input, a second controlled Phase 3 study, C119, was conducted in subjects with HIV-PN.

- Pre-NDA Meeting - 06 March 2008: Meeting objectives included the discussion of the content and format of the NDA filing for PHN and HIV-PN.

    - The pre-meeting background package included information on the clinical development program of the Capsaicin 8% Patch for HIV-PN. At the meeting, NeurogesX sought concurrence on the NDA content and submission plan for both PHN and HIV-PN. Following the meeting, NeurogesX made the decision to pursue an NDA for PHN alone since the second Phase 3 study for HIV-PN had only recently been unblinded and NeurogesX needed more time to further evaluate the HIV-PN data.

- Pre-NDA Meeting - 07 October 2010: Meeting objectives included the discussion of the content and format of a supplemental NDA (sNDA) filing for HIV-PN.

    - The Agency indicated that the content of the proposed sNDA for HIV-PN was adequate for filing. After discussion of the efficacy findings from Studies C107 and

C119, the Division acknowledged that a 30-minute dosing regimen with a more balanced benefit/risk profile might be more desirable than a 90-minute regimen with increased risks. However, NeurogesX must provide data and a strong argument supporting the 30-minute dose. With regard to safety, the Agency stated that the sNDA appeared to satisfy the safety database requirement. NeurogesX needed to include their rationale for how safety data in other patient populations (i.e., PHN) would be supportive for HIV-PN. The Agency confirmed that additional dermal safety studies in the HIV-PN population were not necessary; however information about the risk for cutaneous sensitization and irritation must be included in the product label.

1.2 Proposed Label Summary for Dosage Administration in HIV-PN

The recommended dose of the Capsaicin 8% Patch for HIV-PN is a single, 30-minute application of up to four patches applied to the most painful skin areas (i.e., a maximum of 4 patches x 280 cm^2 each). Treatment with the Capsaicin 8% Patch may be repeated every three months or as warranted by the return of pain (but not more frequently than every three months). As is the case for the PHN indication, only physicians or health care professionals under the close supervision of a physician can apply the Capsaicin 8% Patch to HIV-PN patients.

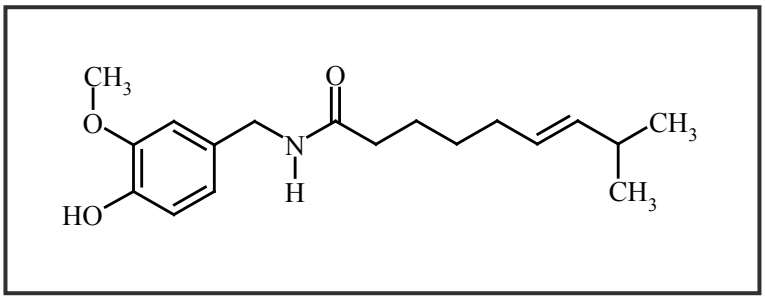
2. Pharmacology and Nonclinical Overview of Capsaicin 8% Patch

2.1 Overview of Capsaicin Mechanism of Action

Capsaicin (*trans*-8-methyl-N-vanillyl-6 nonenamide; 6-nonenamide, N-[(4-hydroxy-3-methoxyphenyl) methyl]-8 methyl-, (6E)) is the active pharmaceutical ingredient contained in Capsaicin 8% Patch. Although there are two geometric isomers of capsaicin, only *trans*-capsaicin occurs naturally [Cordell 1993].

The chemical structure of capsaicin is shown in Figure 1.

Figure 1 Chemical Structure of Capsaicin



Capsaicin (which in this Briefing Document is used to refer to *trans*-capsaicin) is the most abundant pungent molecule contained in spicy foods such as chili peppers. The capsaicin content of chili peppers ranges from 0.1% to 1% w/w [Govindarajan 1991]. In addition to its role as a food constituent, there is substantial human experience with capsaicin in the form of prescription and non-prescription topical analgesics, experimental pain models, and self-defense products (e.g., pepper spray).

The TRPV1 is a ligand-gated, non-selective cation channel preferentially expressed on small diameter sensory neurons, especially nociceptors that detect painful or noxious sensations. Accordingly, TRPV1 is expressed in unmyelinated C-fibers and small myelinated A-fibers [Szolcsanyi 2004]. Following exposure to capsaicin, cutaneous nociceptors become less sensitive to a variety of stimuli, including further capsaicin exposure or thermal stimuli [Szallasi 1999]. A reduction in spontaneous and evoked painful sensations results from topical capsaicin exposures. The effects of topical capsaicin on nociceptor activity have been referred to as ‘desensitization’ and are the rationale for the development of various topical capsaicin formulations for the management of chronic pain syndromes [Holzer 2008; Anand 2011].

2.2 Nonclinical Overview

Capsaicin is the active pharmaceutical ingredient contained in the Capsaicin 8% Patch. NeurogesX has completed a series of GLP-compliant nonclinical safety studies appropriate for the safety evaluation of the compound; these include single-dose (rats and dogs) and 4-week repeated-dose (rats and pigs) studies.

Topical capsaicin is well tolerated, as no capsaicin- or Capsaicin 8% Patch-related toxicity has been noted in any species, with the possible exception of slightly increased incidence of skin lesions and mild erythema at the high-dose level in the repeated-dose rat study. A low incidence of mild sensitization was seen in a dermal study with guinea pigs. A battery of four mutagenicity studies has been conducted using capsaicin and includes three *in vitro* studies and an *in vivo* p.o. micronucleus test in the mouse. No evidence of mutagenicity or clastogenicity was observed.

2.3 Pharmacokinetics

2.3.1 Systemic Exposure

Systemic exposure to capsaicin was assessed in HIV-PN subjects in Study C107 after Capsaicin 8% Patch treatments of 60 minutes (n = 22) and 90 minutes (n = 37) using a high-performance liquid chromatography with MS/MS detection bioanalytical assay (lower limit of quantification [LLOQ] = 0.5 ng/mL). Assays for the major capsaicin metabolites 16-hydroxy-capsaicin (M1), 16,17-dehydro-capsaicin (M2), and 17-hydroxy-capsaicin (M3) were also performed, as well as determination of plasma lidocaine concentrations (LLOQ = 0.5 ng/mL for all metabolites and lidocaine). Blood samples were taken prior to and 60 minutes after anesthetic application, immediately after patch removal, and 1 and 3 hours after patch removal.

No quantifiable capsaicin levels (i.e., > 0.5 ng/mL) were observed at any time point after 60-minute Capsaicin 8% Patch treatments (n = 22). In 3 of the 37 subjects (8%) with HIV-PN who were studied after a 90-minute Capsaicin 8% Patch treatment, quantifiable capsaicin levels (i.e., >0.5 ng/mL) were observed (i.e., 0.57 to 1.75 ng/mL). Of these 3 subjects, 2 had treatment areas >750 cm^2, and one had a treatment area between 500 and 750 cm^2. A maximum systemic level of 1.75 ng/mL was detected 1 hour after patch removal in one subject with a treatment area of 924 cm^2. No capsaicin metabolites were detected in any plasma sample in Study C107.

The capsaicin maximum plasma concentration (C_{max}) of 1.75 ng/mL observed following a 90-minute Capsaicin 8% Patch application is similar to reported plasma capsaicin levels observed after dietary ingestion of capsaicin (contained in peppers). In a published study of plasma capsaicin concentrations in healthy volunteers following the dietary ingestion of 5 grams of standardized chili peppers, containing approximately 27 mg of capsaicin, the average C_{max} was 2.5 ng/mL, or 8.1 nM [Chaiyasit 2009]. This dietary dose of capsaicin was well tolerated and it is an amount of capsaicin that is believed to be typical of the daily dietary intake of capsaicin in countries such as India, Thailand and Mexico [Committee of Experts on Flavouring Substances 2005]. In addition, the plasma half-life of capsaicin is approximately 25 minutes following oral administration [Chaiyasit 2009] and about 98-minutes when delivered through the skin by Capsaicin 8% Patch [Babbar 2009].

Therefore, the level of systemic capsaicin exposure in humans following Capsaicin 8% Patch applications of 90 minutes or less is below systemic levels observed following ingestion of a standardized meal containing approximately 27 mg capsaicin [Chaiyasit 2009].

2.3.2 Metabolism

Capsaicin in the systemic circulation is highly bound to plasma proteins (93% to 94% in humans; Study 7215-143) and undergoes significant and rapid hepatic metabolism [Chanda 2008]. A human liver microsome metabolic assay identified three major capsaicin metabolites: 16-hydroxy-capsaicin, 16,17-dehydro-capsaicin, and 17-hydroxy-capsaicin (Study 7215-125); these metabolites are in agreement with those reported by others [Reilly 2005].

An *in vitro* metabolism study using human skin (Study 274-1060-01) demonstrated that the *in vitro* biotransformation of capsaicin in human skin is slow and minimal. Although capsaicin was metabolized to vanillylamine and vanillic acid, the majority of the sample radioactivity was associated with unchanged capsaicin. This suggests that cutaneous capsaicin is not metabolized rapidly and can display a persistent pharmacological activity in the skin, which is the site of action. The half-life of topically administered capsaicin in the stratum corneum has been estimated to be about 24 hours [Pershing 2004].

2.4 Clinical Pharmacodynamics

In a Phase 1 volunteer study (Study C101) of effects on epidermal nerve fiber density (ENFD) and sensory function, treatment with the Capsaicin 8% Patch for 60 or 120 minutes resulted in significantly lower mean nerve fiber densities (as measured by protein gene product [PGP] 9.5 immunostaining) at Day 7 (4.8 and 4.4 neurites/mm, respectively) than sites treated with either

placebo (12 neurites/mm; $P < 0.001$ for both comparisons) or the low-dose Control patch for 120 minutes (11 neurites/mm; $P < 0.01$ for both comparisons) [Malmberg 2004].

Capsaicin 8% Patch for 60 or 120 minutes was associated with a small, but significant, reduction in warmth sensitivity (i.e., higher warmth detection threshold) on Day 7 (+1.9°C and +1.1°C, respectively). However, only the skin sites exposed for 60 minutes showed a significant difference from placebo-treated sites in mean change from Baseline data. There were no significant within-treatment or between-treatment effects for sensitivity to cold. In a second Phase 1 volunteer study (Study C115), 60-minute treatment with the Capsaicin 8% Patch resulted in an 80% reduction in ENFD compared with untreated sites at Week 1; by Week 12, a 20% reduction was noted, and by Week 24, nearly full recovery of ENFD was observed [Kennedy 2010].

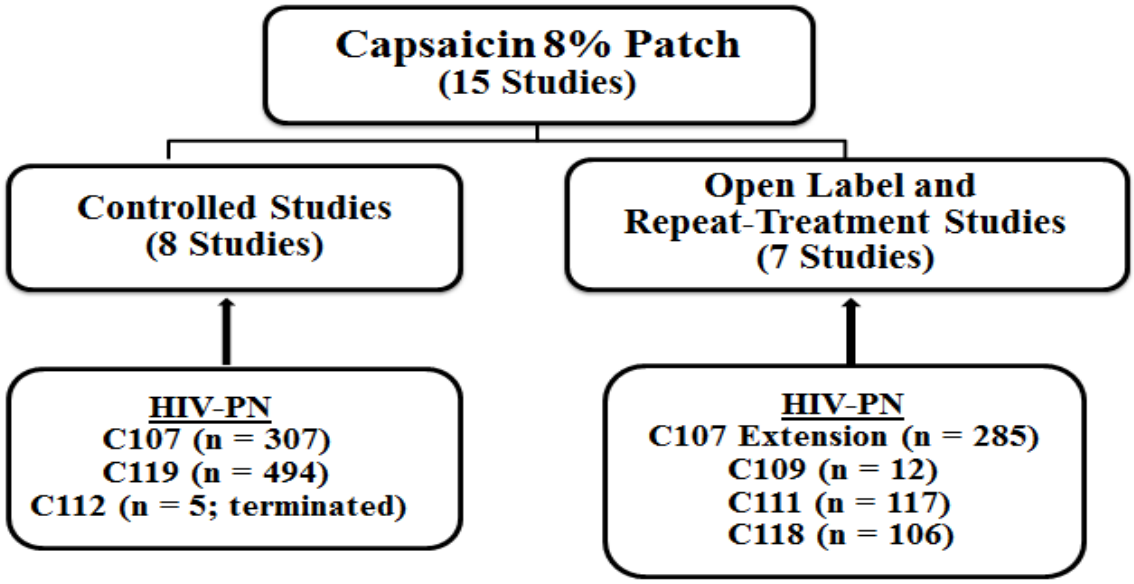
The reduction in ENFD was associated with small, transient alterations in nerve fiber function. At Week 1 following patch removal, subjects experienced a 15% reduction from Baseline in the number of sharp stimuli detected as “sharp”, whereas untreated sites were essentially unchanged. The effect on sharp pain perception normalized by Week 12, which correlates with the recovery of ENFD from Week 1 (80% reduction) to Week 12 (20% reduction). One week after exposure, the mean tactile threshold increased by approximately 8% from 4.07 mN at Baseline to 4.39 mN at Capsaicin 8% Patch-exposed sites ($P = 0.02$ compared to low-dose Control). The effect on tactile thresholds normalized by Week 12, and tactile thresholds were similar in exposed and control skin areas at Weeks 12 and 24. No differences in heat pain thresholds and the mean cooling thermal thresholds determined by quantitative sensory testing (QST) were seen at Weeks 1, 12, or 24 following Capsaicin 8% Patch treatment.

Taken together, the results of pharmacodynamics studies suggest that a single 60- to 120-minute application of Capsaicin 8% Patch has the potential to reduce ENFD in healthy volunteers without clinically significant adverse effects on protective sensory function (e.g., the ability to detect heat, cold, sharp, and tactile sensations). The reduction in ENFD and the minor sensory changes were fully reversible and returned to Baseline levels without change in nervous system function within 3 to 6 months following patch removal.

3. Overview of Capsaicin 8% Patch Clinical Development Program

The Capsaicin 8% Patch clinical development program for neuropathic pain has consisted of a total of 15 clinical trials: two Phase 1 studies in healthy volunteers (Studies C101 and C115) and 13 Phase 2 or Phase 3 clinical studies in subjects with HIV-PN, PHN, and painful diabetic peripheral neuropathy (DPN) (also referred to as painful diabetic neuropathy or PDN). Figure 2 summarizes all of the 15 clinical studies of Capsaicin 8% Patch for the treatment of neuropathic pain.

Figure 2 **Overview of All Capsaicin 8% Patch Clinical Studies in Neuropathic Pain**



HIV-PN = human immunodeficiency virus-associated peripheral neuropathy

NOTES:

Studies C107 included a 12-week, double-blind phase followed by a 40-week, open-label, repeat-treatment extension phase.

Study C112 was terminated after having enrolled only 5 subjects (3 receiving Capsaicin 8% Patch and 2 receiving low-dose Control) due to the both an initial review of the data from Study C107 that showed that the 60-minute Capsaicin 8% Patch application was not significantly superior to the low-dose Control and to the business conditions at the time.

3.1 HIV-PN Studies

The efficacy and safety of Capsaicin 8% Patch in subjects with painful HIV-PN has been evaluated in 6 clinical studies: C107, C119, C112, C109, C111, and C118. The study design and methodology of these clinical studies are summarized in Appendix C. Three of the studies were open-label and 3 were controlled trials.

Of the 3 controlled studies, two Phase 3 multicenter, randomized, double-blind studies were designed to evaluate the efficacy and safety of the Capsaicin 8% Patch in painful HIV-PN. Efficacy and safety results from pivotal Study C107 and Study C119 are described in detail in Sections 4 and 5, respectively. In each of these studies, a low-dose capsaicin Control was used.

The third controlled HIV-PN Study (C112) was designed to evaluate a single 60-minute Capsaicin 8% Patch application. However, Study C112 was terminated after enrollment of 5 subjects (3 receiving Capsaicin 8% Patch and 2 receiving low-dose Control). The early termination of this study was due to both an initial review of the data from Study C107 (that showed that the 60-minute Capsaicin 8% Patch application was not significantly superior to the low-dose Control) and to the business conditions at the time. Due to the early termination of the study, no efficacy data were analyzed. Only limited or uncontrolled efficacy data from Studies C109, C111, and C118 were collected. Study C109 was a single-dose, uncontrolled, open-label pilot study in 12 subjects with HIV-PN. Study C111 was a single-dose, uncontrolled, open-label study that enrolled subjects with PHN, PDN, and only one subject with HIV-PN. Study C118 was an open-label, uncontrolled, repeat-treatment safety study that enrolled subjects with HIV-PN or PHN. Therefore, efficacy data from these studies will not be discussed further in this Briefing Document.

3.1.1 Low-Dose Control Patch

A low-dose (capsaicin) Control patch was used in place of a placebo patch in an attempt to provide effective blinding of the studies, since topical capsaicin can produce a local burning sensation. The low-dose Control patch used in Studies C107 and C119 looked identical to the Capsaicin 8% Patch but contained a lower concentration of the active ingredient, capsaicin (0.04% w/w capsaicin; 3.2 µg/cm^2). Capsaicin delivery from the low-dose (capsaicin) Control patch is approximately 29-fold less than from Capsaicin 8% Patch (when both are applied for 60 minutes) (Study VAL-07-002-R). This lower dose of topical capsaicin had no significant effect on nerve fiber density or sensory function following application times as long as 120 minutes (Study C101).

Of note, the low-dose Control patch produced some of the local side effects of therapy (e.g., pain, erythema) so that the treatment blind could not be reliably broken based upon an individual subject's initial reaction to treatment. Subjects in both treatment groups experienced erythema, and a significant number of low-dose Control subjects also experienced treatment-related pain. Further evidence of effective blinding was provided by the day-by-day analysis of NPRS scores, which showed that the Capsaicin 8% Patch treatment effect was not driven by

early differences, as might be expected due to ineffective blinding. Together, these data support the conclusion that the low-dose (capsaicin) Control patch provided adequate blinding, maintaining the integrity of the pivotal double-blind study results.

4. Study C107 of Capsaicin 8% Patch in HIV-PN

4.1 Study C107 Design

Study C107 was a Phase 3, randomized, double-blind, controlled, multicenter pivotal study comparing the efficacy, safety and tolerability of the Capsaicin 8% Patch, applied for 30, 60, or 90 minutes, for the treatment of painful peripheral neuropathy resulting from HIV infection and/or antiretroviral drug exposure. The study consisted of a 12-week double-blind period followed by a 40-week open-label extension phase, during which subjects were eligible to receive up to three open-label treatments, no more frequently than 12 weeks apart. Re-treatments during the open-label phase were optional and based on persistence of pain (i.e., less than 25% improved compared to the Baseline of the double-blind phase) or a return of pain (i.e., greater than 20% increase compared to the average pain score during Weeks 2 and 3 following initial double-blind treatment). Therefore, the total duration of this study was 52 weeks, plus a preceding Screening period of 7 days.

Eligible subjects had moderate to severe neuropathic pain (defined as an average NPRS scores of 3 to 9, inclusive, during Screening) associated with HIV disease and/or antiretroviral toxic neuropathy in both feet. Painful areas with a combined total surface area of up to 1000 cm^2 across both feet were treated.

At Screening, treatment areas were identified based on the presence of spontaneous and evoked pain determined by a sensory examination performed by the Investigator. The treatment areas were identified as the areas formed by a line drawn around the dorsal, lateral, plantar, and medial aspects of the foot that enclosed the most proximal level of painful symptoms and all distal areas of the foot, including the outer surfaces of the toes, on each foot. The boundaries of the treatment areas were marked on each foot with a skin-marking pen. The patches were supplied in a single patch size and were cut to fit the painful areas. The treatment areas were limited to a combined maximal estimated total surface area of approximately 1000 cm^2 across both feet.

The initial Treatment Visit generally occurred 1 week after Screening. Prior to study treatment application, subjects received pre-treatment with a topical local anesthetic cream (LMX4 ™, lidocaine 4%) for 60 minutes in an attempt to offset treatment-related discomfort or pain resulting from capsaicin. Following the local anesthetic pre-treatment, capsaicin patches were applied to the designated painful areas for 30, 60, or 90 minutes, as assigned by randomization. During the open-label phase, all subjects eligible for re-treatment received Capsaicin 8% Patch

applied for 60 minutes. After completion of the assigned treatment time, the patches were removed and the treatment areas were cleansed using a study-supplied cleansing gel followed by soap and water to remove residual capsaicin from the skin. Subjects were monitored for at least 2 hours following treatment before being discharged and were asked to return for follow-up visits at Weeks 1, 4, and 12. Subjects entering the open-label extension were scheduled for follow-up at Weeks 24, 36, and 52 (Termination Visit).

Each evening throughout the study, subjects used a pain diary to record the Numeric Pain Rating Scale (NPRS) to rate the "average pain for the past 24 hours" for their painful area(s). The NPRS is an 11-point scale (0 to 10), with 0 indicating no pain and 10 indicating worst possible pain [Farrar 2001]. Efficacy was also evaluated by periodic assessments of pain using the Gracely Pain Scale, Patient and Clinical Global Impression of Change (PGIC/CGIC), Brief Pain Inventory Short Form (BPI), Self-Assessment of Treatment (SAT), and Short-Form McGill Pain Questionnaire (SFMPQ).

Subjects were allowed to remain on stable chronic analgesic medication regimens during the study, but were not allowed to use any topical analgesic medications on the affected areas. Subjects could receive concomitant medications including opioids, if administered orally or transdermally at a total daily dose not exceeding morphine 60 mg in Study C107. No p.r.n. (pro re nata; taken as needed) pain medications were allowed during the trial except for short-term use of opioid-based oral pain medications between Day 0 and Day 7, and acetaminophen or aspirin up to 2 g/day or ibuprofen up to 600 mg/day, as needed for aches and pain during the study.

Open Label Re-treatments

Following completion of the 12-week double-blind portion of the study, subjects were eligible to enter a 40-week open-label extension where they received up to three 60-minute Capsaicin 8% Patch treatments, irrespective of the treatments received at the double blind, at Weeks 12, 18, 24, 30, 36 and/or 42, as warranted by the persistence of or return of pain scores toward baseline as calculated using the following criteria:

- The recent average pain score (mean of "average pain for the past 24 hours" during the past 2 weeks) is less than 25% improved compared to the baseline average pain score (mean of "average pain for the past 24 hours" scores for Days -14 to -1 before initial double-blind treatment on Day 0), OR

- The recent average pain score (as above) is more than 20% increased compared to the average pain score during Weeks 2 and 3 (mean of "average pain for the past 24 hours" for Days 8 to 21 following initial double-blind treatment on Day 0).

Subjects had at least 2 weeks of diary scores showing return of pain before re-treatment. The interval between re-treatments had to be 12 weeks.

All open-label re-treatments were to be in the same general location as the initial double-blind treatment. However, subjects were randomly assigned in a 1:1 ratio to receive either:

- Re-treatment over the area in which subject received initial double-blind treatment, plus any additional currently painful areas (if applicable), or
- Re-treatment only in the currently painful areas at the time of re-treatment evaluation.

In either case, the re-treatment area was limited to a combined estimated total surface area of approximately 1000 cm^2 across both feet. Open-label re-treatment group randomization was confirmed by NeurogesX at the time of re-treatment authorization.

4.1.1 Study Centers and Patient Population

A total of 300 subjects were planned (see Section 4.2.1.1) for this study and 307 subjects from 32 study centers in the United States were actually enrolled.

4.1.2 Neurological Examinations for Safety and Tolerability

Targeted neuropathy examinations at the areas treated were performed at Screening, Treatment Visit, and at Weeks 1, 4, 12, 24, 36, and 52 to identify clinically relevant deficits in sensory function at baseline and to re-assess for the presence of such deficits following investigational treatment with Capsaicin 8% Patch. Quantitative Sensory Testing (QST) was done at selected sites at Screening and at Weeks 4, 12, and 52 to measure warm/cool thermal and vibration perception thresholds. Nerve conduction evaluations were also performed at selected sites at Screening and at Weeks 12 and 52. Measurements of sensory nerve function (sural nerve amplitude, latency, and conduction velocity) and motor nerve function (peroneal nerve amplitude, latency, and conduction velocity) were assessed via electrical stimulation of the subject's lower extremity. Results of these evaluations were interpreted by a qualified clinical neurophysiologist at a study-specified central laboratory.

4.1.3 Primary Endpoint

The primary efficacy endpoint for the pivotal Study C107 was the percent change in "average pain for past 24 hours" (i.e., the average daily pain score recorded each evening by the subject) in the treated area(s), as assessed by daily NPRS score from Baseline to Weeks 2 to 12 (i.e., from Days 8 through 84). This average-over-time approach (i.e., the average daily score from Weeks 2 to 12) was the prespecified primary endpoint and was used to assess the efficacy of Capsaicin 8% Patch during the 12-week study period. This average-over-time approach did not include Week 1 scores in order to avoid the potential for bias from the protocol-permitted use of p.r.n. analgesics during the first study week for treatment-related pain.

Of note is the fact that in most chronic pain studies, a Week 12 landmark analysis is typically employed to assess treatments intended for chronic pain conditions. However, most chronic pain treatments are administered at regular daily dosing intervals over a 3-month assessment period, with their clinical effect related directly to their plasma levels. Therefore, if this endpoint were to have been used for the current studies, a Week 12 analysis would measure only the residual effect of a single Capsaicin 8% Patch treatment that had been administered 12 weeks earlier. Given these important differences in treatment schedule between most current neuropathic pain medications and the Capsaicin 8% Patch, the average-over-time approach (during Weeks 2 to 12) provides a more relevant efficacy assessment for the Capsaicin 8% Patch. This endpoint was therefore selected to best evaluate the unique characteristics of the Capsaicin 8% Patch, which was administered only once in the controlled 12-week observation period.

At each visit, subjects received a take-home, paper-based daily diary to record the Numeric Pain Rating Scale (NPRS) scores. Each evening throughout the study, subjects used this take-home, paper-based daily diary to record their NPRS scores to rate their "average pain for the past 24 hours" for their painful area(s). The NPRS is an 11-point scale (0 to 10), with 0 indicating no pain and 10 indicating worst possible pain [Farrar 2001]. Subjects were asked to complete the daily diary at approximately 9 PM to record NPRS scores for present pain intensity ("pain now"), worst pain for past 24 hours, and average pain for past 24 hours. Between the Screening Visit and the day of investigational treatment, the Coordinator contacted each subject for follow-up and to assure diary compliance. If any pain medication other than what the subject was taking at the time of screening was used during the study, it was recorded by subjects in the daily take-home pain diary and/or in their source documentation, and recorded on the Concomitant Medication CRF during the next study visit.

In addition, landmark analyses of the Week 12 data are presented to provide evidence of the durability of the treatment effects and to permit comparison with the results of trials of other neuropathic pain treatments.

4.1.4 Secondary Endpoints

Secondary efficacy endpoints included:

(1) Proportion of responders (i.e., subjects who achieved ≥30% decrease in mean "average pain for the past 24 hours" NPRS score from Baseline) during Weeks 2 to 12, within each treatment group;

(2) Change in weekly mean percent in the "average pain for the past 24 hours" NPRS score from Weeks 2 to 4 and 2 to 8, respectively, from Baseline, within each treatment group;

(3) Change in Gracely Pain Scale scores from Baseline to Week 12. Using the Gracely Pain Scale [Gracely 1978], subjects rated their average pain during the preceding 24 hours using a pain descriptor, which was then assigned a numerical value.

(4) Change in BPI from Screening to Week 12 was analyzed in this study. The Brief Pain Inventory (BPI) [Daut 1983] is an index of pain severity, pain relief, and the effects of pain on the subject's ability to function. A modified Version of the BPI (See Appendix D) was used in this study.

(5) Change in Short-Form McGill Pain Questionnaire (SFMPQ) [Melzack 1987] was analyzed in this study. The SFMPQ was collected at Screening and at the Week 1, 4, 12, and 52 study visits. The SFMPQ consists of 15 descriptors (11 sensory, 4 affective) for which subjects were asked to rate their pain on an intensity scale as 0 = none, 1 = mild, 2 = moderate or 3 = severe (Appendix D). Three pain scores are derived from the sum of the intensity rank values of the words chosen for sensory, affective, and total descriptors. The SFMPQ also asks subjects to identify their Present Pain Intensity (PPI) on a scale of 0 = no pain to 5 = excruciating pain.

(6) The Patient Global Impression of Change (PGIC) was summarized by comparing all 7 response options at Week 12 as well as the active groups to the low-dose Control group for the proportion of subjects reporting improvement ("slightly improved", "much improved", and "very much improved"). The PGIC provides a global assessment of patient improvement using a 7-point scale (details in Appendix D) that is recommended in

chronic pain studies [Dworkin 2005] and has been shown to be more sensitive to treatment effects in neuropathic pain than pain intensity measurements [Haanpää 2011]. The PGIC was measured at Weeks 1, 4, 12, and 52.

(7) Clinical Global Impression of Change (CGIC) was collected at Weeks 1, 4, and 12. It provides a global assessment of patient improvement by clinicians on a 7-point scale (details in Appendix D). The Week 12 responses were summarized and compared between the active groups and low-dose Control group for the proportion of subjects reporting improvement ("slightly improved," "much improved," and "very much improved").

(8) For the Subject Self-Assessment of Treatment (SAT) (Details in Appendix D), subjects were asked five questions about their assessment of treatment at their Week 12 and Week 52 study visits. Responses to the SAT at Week 12 were summarized within each group and compared between the active and the low-dose Control groups.

4.2 Clinical and Statistical Methodology

4.2.1 Statistical Methods

This section describes the prespecified statistical analyses methods for Study C107.

4.2.1.1 Sample Size and Statistical Powering

A sample size of 300 subjects for Study C107 was determined based on a two-sided Student's t-test to detect a difference of 15% change from Baseline in NPRS scores between the pooled Capsaicin 8% Patch treatment and pooled low-dose control group, at a 0.05 significance level and with 90% power. Subjects were randomized in a 3:3:3:1:1:1 allocation scheme (Capsaicin 8% Patch for 90, 60, and 30 minutes and low-dose Control for 90, 60, and 30 minutes).

4.2.1.2 Analysis Populations

All efficacy parameters were assessed in the Intent-to-Treat (ITT) population. In Study C107, the ITT population included all subjects who were randomized, received study treatment, and had at least 3 days of non-missing "average pain for the past 24 hours" NPRS scores for the calculation of a Baseline average score. Unavailability of any post-treatment pain scores were not a criterion for exclusion from the ITT population. Subjects were analyzed as randomized.

4.2.1.3 Primary Statistical Analysis

Calculation of Baseline Score

Baseline average scores used in the primary endpoint analysis were calculated by taking the average of the daily NPRS scores up to the day prior to the day of the treatment. The C107 protocol allowed certain changes of concomitant pain medications up to the day of the screening visit. It stipulated that, if such changes were made, the normal screening period of one week should be prolonged by two additional weeks in order to ensure a reliable baseline period.

Prespecified Primary Endpoint Analysis

The prespecified primary endpoint in Study C107 was the percent change from Baseline in the "average pain for the past 24 hours" NPRS score during Weeks 2 to 12. As previously described, a modified average-over-time approach (average from Weeks 2 to 12) was prespecified and used to assess the efficacy of Capsaicin 8% Patch during the 12-week controlled study period due to unique characteristics of Capsaicin 8% Patch.

In the prespecified primary endpoint analysis, treatment groups were compared using a gender-stratified ANCOVA model adjusting for Baseline average NPRS scores, the pain reduction percent change resulting from pre-treatment topical anesthetic (LMX4®, 4% lidocaine) application, and the NPRS score immediately prior to the LMX4 application as covariates. The rationale for using pre-LMX4 pain score and percent change in pain score after LMX4 treatment as covariates in the ANCOVA of percent change in NPRS scores from Baseline was that in the Capsaicin 8% Patch studies of PHN, pain intensity was observed to decrease following a 60-minute application of the topical anesthetic LMX4.

A gender-stratified ANCOVA model was used because a difference in treatment response by gender was observed in PHN studies: male subjects reported smaller reductions in pain scores than female subjects in both the Capsaicin 8% Patch group (-21.5% and -32.7%, respectively) and low-dose Control group (-12.9% and -21.7%, respectively) [Webster 2010].

Gender stratification was calculated as follows:

1. The covariates adjusted treatment differences, D_m and D_f, were calculated for male subjects and female subjects, respectively.

2. The sample size weighted overall treatment difference, D, was calculated as $D = w_m D_m + w_f D_f$; where gender weight, $w_m = n_m / n$ and $w_f = n_f / n$, was determined by the proportion of males and females in the ITT population. Additionally, n_m was the number of male subjects, n_f was the number of female subjects, and $n = n_m + n_f$.

In Study C107, through prespecified analysis, the Capsaicin 8% Patch dose groups were compared with the total low-dose Control group using a hierarchical testing procedure, beginning with an overall comparison of all Capsaicin 8% Patch dose groups combined, followed by the 90-minute, 60-minute, and 30-minute Capsaicin 8% Patch dose groups, as described below.

First, a null hypothesis (H_0) of "There is no difference between the total Capsaicin 8% Patch group and the total low-dose Control group in the mean percent change" was tested at the 0.05 significance level.

Second, if the first null hypothesis (H_0) was rejected, then the Capsaicin 8% Patch dose groups were to be compared with the pooled low-dose Control group using the following hierarchical testing procedure:

- H_{01}: "There is no difference between low-dose Control and the Capsaicin 8% Patch 90-minute dose group in the mean percent change"
- H_{02}: "There is no difference between low-dose Control and the Capsaicin 8% Patch 60-minute dose group in the mean percent change"
- H_{03}: "There is no difference between low-dose Control and the Capsaicin 8% Patch 30-minute dose group in the percent change"

The test procedure was designed to first investigate, at a significance level of 0.05, whether H_{01} could be rejected. In case H_{01} was rejected, then hypothesis H_{02} would be tested at a significance level of 0.05. If H_{02} was rejected, then hypothesis H_{03} would be tested at a significance level of 0.05.

This ordering of hypotheses, known as a gate-keeping strategy to maintain the overall study type-I error equal to 5%, assumed a linear monotonic dose response (in terms of patch application times) with the assumption that the 90-minute application dose would have better efficacy than the 60-minute application dose, which in turn was assumed to have better efficacy than the 30-minute application dose. This method allowed for a test at the significance level of 0.05 for each of the individual hypotheses, unless the previous hypothesis could not be rejected.

Since the low-dose Control arms also had different patch application durations, a test of homogeneity was planned to evaluate the homogeneity and poolability of the low-dose Control groups.

4.2.1.4 Handling of Missing NPRS Scores

The handling of missing data is a challenge in clinical trials, especially analgesic studies. Approaches such as Last Observation Carried Forward (LOCF) and Baseline Observation Carried Forward (BOCF) have been used but each has significant limitations. Recently, a panel was convened by the National Academy of Sciences/National Research Council which concluded that "Single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified" [National Research Council 2010].

The prespecified approach utilized in the Capsaicin 8% Patch program for the handling of missing data was a modified LOCF approach, which combined the assumptions of a BOCF analysis during the first week following treatment with the LOCF approach after the first week as follows:

- If the NPRS score was missing on any of Days 0 to 8 or missing on Day 8 and 1 or more consecutive days, then the Baseline score was imputed for those days.
- If the NPRS score was missing for any day past Day 8, then the missing score was imputed by the latest available non-missing score collected before that day.
- If all post treatment NPRS scores were missing (including Day 0) then all scores were imputed by the Baseline score.

The rationale for this approach was based on the fact that the Capsaicin 8% Patch is administered as a single treatment with only minimal, brief systemic exposure in a minority of

subjects and a median duration of application site reactions of 3 days or less. Therefore, missing data from subject discontinuations or otherwise due to drug-related adverse effects were most likely to occur during the first week following exposure. Thus, NPRS scores missing on any of Days 0 to 8 or missing on Day 8 and 1 or more consecutive days were imputed using a BOCF approach. After the first week, missing data was largely expected to be "missing at random" while recognizing that some missing data, such as drop outs due to lack of response, were likely "missing not at random" due to the expected efficacy of the study treatment and higher incidence of drop outs due to lack of response in the low-dose Control group. Thus, imputing missing values in this instance with the last observation would be unlikely to bias the estimation of the treatment effect in a favorable direction compared to the use of a baseline imputation method.

In addition, the following algorithm will be applied: for all patients who answered 'Yes' to completion of study but have a termination date within the Week 12 window (Days 78 to 84), values will not be imputed for days in the Week 12 window following the last diary entry date. All other cases will be imputed through Day 84.

In addition to the use of the modified LOCF imputation method, results using a BOCF approach were also provided as a sensitivity analysis. For the BOCF approach, if an NPRS score was missing on any post treatment day (including Day 0), then the Baseline score was imputed for that day.

Non-imputed (or the complete case) analyses were also performed for the primary and key secondary endpoints.

4.2.1.5 Sensitivity Analyses

An additional exploratory analyses methods of the primary endpoint is provided in Appendix E.

4.2.2 Secondary Endpoints Analyses

For proportion of responders (i.e., subjects who achieved ≥30% decrease in mean "average pain for the past 24 hours" NPRS score from Baseline) during Weeks 2 to 12, treatment differences were compared by using the gender stratified logistic regression with Baseline pain score, pre-LMX4 pain score, and percent change in pain score after LMX4 treatment as covariates. In addition, the odds ratio of observing responses in the Capsaicin 8% Patch group compared with the low-dose Control group, and its 95% CI, were estimated.

Weekly mean percent changes in the "average pain for the past 24 hours" NPRS score from Baseline through Week 12 were plotted for each week and compared among each treatment groups.

Each Capsaicin 8% Patch group was compared to the pooled low-dose Control group for change from Baseline to Week 12/Termination for Gracely Pain Score, BPI, and SFMPQ and Wilcoxon (Rank Sum) test for PGIC, CGIC, and SAT.

4.2.3 Efficacy of Repeated Treatment

Subjects in Study C107 who completed study evaluations through Week 12 had the option of receiving up to three additional open-label 60-minute Capsaicin 8% Patch treatments at Weeks 12, 18, 24, 30, 36, and/or 42. Subjects remained blinded to their first treatment throughout the entire 52-week Study C107.

To determine whether Capsaicin 8% Patch was efficacious with repeated treatment, efficacy data were summarized using the following approaches:

- The mean percentage change from Baseline in the "average pain for the past 24 hours" NPRS score during Weeks 2 to 12 after each Capsaicin 8% Patch treatment was summarized by the total number of Capsaicin 8% Patch treatments received.

Subjects in the category of "1 Capsaicin 8% Patch treatment" included both those who received a double-blind Capsaicin 8% Patch treatment but no retreatment during the open-label phase and those who received double-blind low-dose Control treatment and then received 1 open-label Capsaicin 8% Patch treatment.

Time to First Retreatment

The median time to first open-label treatment in Study C107 was estimated by Kaplan-Meier survival analysis and compared between treatment groups using a Log Rank Test. Subjects without retreatment were considered to be censored at the last available (i.e., non-missing) NPRS diary date to maintain the ITT analysis.

4.3 Study C107 Results

4.3.1 Demographic and Other Baseline Characteristics

Table 1 shows demographic and other baseline characteristics of subjects in Study C107. The demographic and other baseline characteristics of subjects in the Capsaicin 8% Patch group (n = 225) were similar to the low-dose Control group (n = 82).

The average age of subjects enrolled in Study C107 was 48 years. The majority of subjects were Caucasian and male. The average Baseline pain level, as measured by NPRS score, was 5.9 for both the total Capsaicin 8% Patch and low-dose Control groups. Most subjects (84% in the total Capsaicin 8% Patch group and 92% in the low-dose Control group) had a treatment area >750 cm^2. At Baseline, approximately 18% of subjects were using neurotoxic antiretrovirals (e.g. didanosine, zalcitabine stavudine) in both the Capsaicin 8% Patch and low-dose Control groups.

The average duration of HIV-PN was 3.3 years in the Capsaicin 8% Patch group and 3.4 years in the low-dose Control group. Most subjects (69% of Capsaicin 8% Patch and 65% of low-dose Control subjects) were receiving some form of concomitant neuropathic pain treatment at Baseline.

Table 1 Demographic and Other Baseline Characteristics – Study C107

Characteristic	Low-dose Control	Capsaicin 8% Patch			
	Total N = 82	30 min N = 72	60 min N = 78	90 min N = 75	Total N = 225
Mean Age in years (SD)	48 (8)	47 (9)	48 (8)	47 (8)	48 (8)
Gender, n (%)					
Male	79 (96)	63 (88)	73 (94)	71 (95)	207 (92)
Race, n (%)					
Black	18 (22)	23 (32)	21 (27)	14 (19)	58 (26)
Caucasian	50 (61)	42 (58)	46 (59)	48 (64)	136 (60)
Other[a]	14 (17)	7 (10)	11 (14)	13 (17)	31 (14)
Treatment Area, n (%)					
≤ 250 cm^2	0	0	0	0	0
> 250 – ≤ 500 cm^2	2 (2)	5 (7)	1 (1)	3 (4)	9 (4)
> 500 – ≤ 750 cm^2	5 (6)	7 (10)	11 (14)	9 (12)	27 (12)
> 750 cm^2	75 (92)	60 (83)	66 (85)	63 (84)	189 (84)
Mean Duration of Pain in years (SD)	5.1 (3)	4.2 (3)	5.4 (4)	4.4 (3)	4.7 (3)
Mean Baseline Pain Level (SD)[b]	5.9 (2)	5.9 (2)	5.8 (2)	6.1 (2)	5.9 (2)
On Concomitant Pain Medication[c], n (%)	53 (65)	56 (78)	53 (68)	47 (63)	156 (69)
Using Neurotoxic Antiretrovirals[d], n (%)	15 (18)	14 (19)	13 (17)	14 (19)	41 (18)
CD4 ($x10^6$/L), n	74	63	67	68	198
Mean	434	421	396	497	439
SD	280	270	240	290	270
HIV RNA (copies/mL)[e], n	67	58	68	66	192
Mean	39713	25908	160726	21221	72046
SD	116190.0	96860.0	796450	93470	482310
Median	1017	1032	1193	664	1021

HIV = human immunodeficiency virus, NPRS = Numeric Pain Rating Scale, RNA = ribonucleic acid, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor.
[a]Other includes subjects who classified themselves as Asian or as Other.
[b]Baseline pain level was defined as the mean of all non-biased Screening NPRS scores.
[c]Subjects were defined as being on concomitant pain medication if he or she was on an anticonvulsant, non-SSRI antidepressant or opioid that was issued on Day -1 and was taken for a total duration of at least 7 consecutive days.
[d]Subjects were defined as using neurotoxic antiretrovirals if he or she was on neurotoxic antiretrovirals, such as didanosine, stavudine, or zalcitabine, for at least eight weeks prior to the Screening date.
[e]For HIV RNA, values reported as "<400" were replaced with the numeric value 400 and values reported as "<40" were replaced with the numeric value 40.

4.3.2 Disposition

The disposition of subjects participating in the controlled portion of Study C107 is presented in Table 2. Overall, 87% and 89% of Capsaicin 8% Patch and low-dose Control subjects,

respectively, completed the 12-week, double-blind study. The majority of premature termination subjects were "lost to follow up" (Capsaicin 8% Patch: n=15, 7%; low-dose Control: n=4, 5%). Withdrawal due to an adverse event (AE) occurred with 3 subjects (Capsaicin 8% Patch: n=2, <1%; low-dose Control: n=1, 1%), including 2 Capsaicin 8% Patch subjects who withdrew due to treatment-related application site pain.

Table 2 Subject Disposition -- Study C107

Characteristic	Low-dose Control	Capsaicin 8% Patch			
	Total N = 82	**30 min N = 72**	**60 min N = 78**	**90 min N = 75**	**Total N = 225**
Subjects Entered, n	82	72	78	75	225
Subjects Completed, n (%)	71 (87)	65 (90)	70 (90)	66 (88)	201 (89)
Subject Withdrawal Due to: n, (%)					
Adverse Event	1 (1)	0 (0)	2 (3)	0 (0)	2 (< 1)
Unsatisfactory Response n	2 (2)	0 (0)	0 (0)	1 (1)	1 (< 1)
Non-Compliance	0 (0)	0 (0)	0 (0)	1 (1)	1 (< 1)
Lost to Follow-Up	4 (5)	6 (8)	4 (5)	5 (7)	15 (7)
Death	2 (2)	0 (0)	1 (1)	0 (0)	1 (< 1)
Other	2 (2)	1 (1)	1 (1)	2 (3)	4 (2)

4.3.3 Primary Endpoint Analysis

The first prespecified primary endpoint analysis in Study C107 compared the total group of the Capsaicin 8% Patch subjects to the total group of the low-dose Control subjects. This analysis demonstrated a significantly greater reduction in pain for the Capsaicin 8% Patch group compared with the low-dose Control group (-23% versus -11%, respectively; P = 0.0026; Table 3). Therefore, Study C107 provides evidence, based on this prespecified primary endpoint analysis, that the Capsaicin 8% Patch is significantly better than the low-dose Control in reducing pain intensity scores during the 2 to 12-week treatment period.

Next, subjects treated for 90 minutes were assessed compared to the low-dose Control subjects. This analysis also demonstrated a statistically significant reduction in mean percent change from Baseline during Weeks 2 to 12 for the 90-minute Capsaicin 8% Patch subjects compared

with the total group of low-dose Control subjects (-25% versus -11%, respectively; P = 0.0046).

Pain reductions in the Capsaicin 8% Patch 60-minute group were numerically greater than the low-dose Control group (-16% versus -11%, respectively). However, the between-group difference was not statistically significant (P = 0.29).

Therefore, the study's hierarchical testing procedure did not allow prespecified testing to proceed further due to the failure to show statistical significance of the 60-minute arm. As a result, statistical testing for 30-minute dose group was performed as an exploratory analysis. As shown in Table 3, the subjects treated for 30 minutes demonstrated a nominally statistically significant pain reduction (P = 0.0007) in mean percent change from Baseline in the Capsaicin 8% Patch 30-minute dose group (-28%) compared to the low-dose Control group (-11%).

Table 3 Percent Change in NPRS Scores from Baseline during Weeks 2 to 12 – Study C107

NPRS Score	Low-dose Control	Capsaicin 8% Patch			
	Total N = 82	30 min N = 72	60 min N = 78	90 min N = 75	Total N = 225
Baseline					
Mean (SE)	5.9 (0.2)	5.9 (0.2)	5.8 (0.2)	6.1 (0.2)	5.9 (0.1)
% Change from Baseline					
LS Mean (SE)	-10.7 (3.4)	-27.7 (3.6)	-15.8 (3.4)	-24.7 (3.5)	-22.8 (2.0)
95% CI of LS Mean	-17.4, -4.0	-34.9, -20.6	-22.6, -9.06	-31.7, -17.8	-26.8, -18.8
p-value[a]		0.0007[b]	0.291	0.0046	0.0026

ANCOVA = analysis of covariance, LS = Least Squares, NPRS = Numeric Pain Rating Scale, SE = standard error.
Note: Baseline pain level was defined as the mean of all available non-biased Screening NPRS scores. Missing scores on Day 8 were estimated using the Baseline score; missing scores during Days 9 to 84 were estimated using the previous non-missing score.
[a]P-value was computed using gender stratified ANCOVA to test for a difference between the Capsaicin 8% Patch group and the total low-dose Control group, with Baseline pain score, pre LMX4 pain score, and percent change in pain score after LMX4 treatment as covariates.
[b]This is a nominal p-value. Since study's hierarchical testing procedure did not allow prespecified testing to proceed further due to failure to show statistical significance of the 60-minute arm.

Across the three Capsaicin 8% Patch doses evaluated in Study C107, longer durations of patch application (i.e., 30, 60, or 90 minutes) did not result in greater efficacy; as the 95% CIs for all

three treatment groups overlapped (Table 3). As an exploratory analysis, the dose response was tested using the same ANCOVA model that was prespecified as the primary analysis with the inclusion of treatment (Capsaicin 8% Patch versus low-dose Control) by patch duration (30, 60, and 90 minutes) interaction effect in the model. This interaction was not statistically significant with P = 0.323, supporting the conclusion of homogeneity of the differences between the respective doses and their corresponding controls. Thus, all application times evaluated appear to be on the plateau portion of the dose response curve (i.e., there appears to be a flat dose response in terms of patch application times from 30 to 90 minutes). A test of homogeneity of response was additionally performed in the low-dose Control groups and found no significant differences between the low-dose Control groups (P = 0.21). As a result, it was concluded that the 3 low-dose Control arms were homogeneous. Moreover, the 95% CI of the least squares (LS) mean of the percent change from Baseline to Weeks 2 to 12 in NPRS score of the 3 low-dose Control groups were found to be overlapping. Thus, data from the pooled low-dose Control arms were used to compare against each individual Capsaicin 8% patch application time group.

The magnitude of the missing data is low in Study C107. Among the 272 (88.5%) subjects who completed the study, only 38 (14%) subjects missed reporting an NPRS score for a day and, of these subjects, 18 (6.8% of the total subjects) missed reporting NPRS score for two days and 12 (4.3%) subjects missed reporting an NPRS score for 3 or more days. Due to its low frequency, the missing data did not impact the outcome of the primary endpoint.

4.3.4 Secondary Efficacy Endpoints

Significantly greater proportions of subjects in the total, 90-minute, and 30-minute Capsaicin 8% Patch groups experienced a ≥30% response compared with the low-dose Control group (P = 0.0093, P = 0.0085, P = 0.0017; respectively) (Table 4).

Table 4 Proportion of Responders during Weeks 2 to 12 -- Study C107

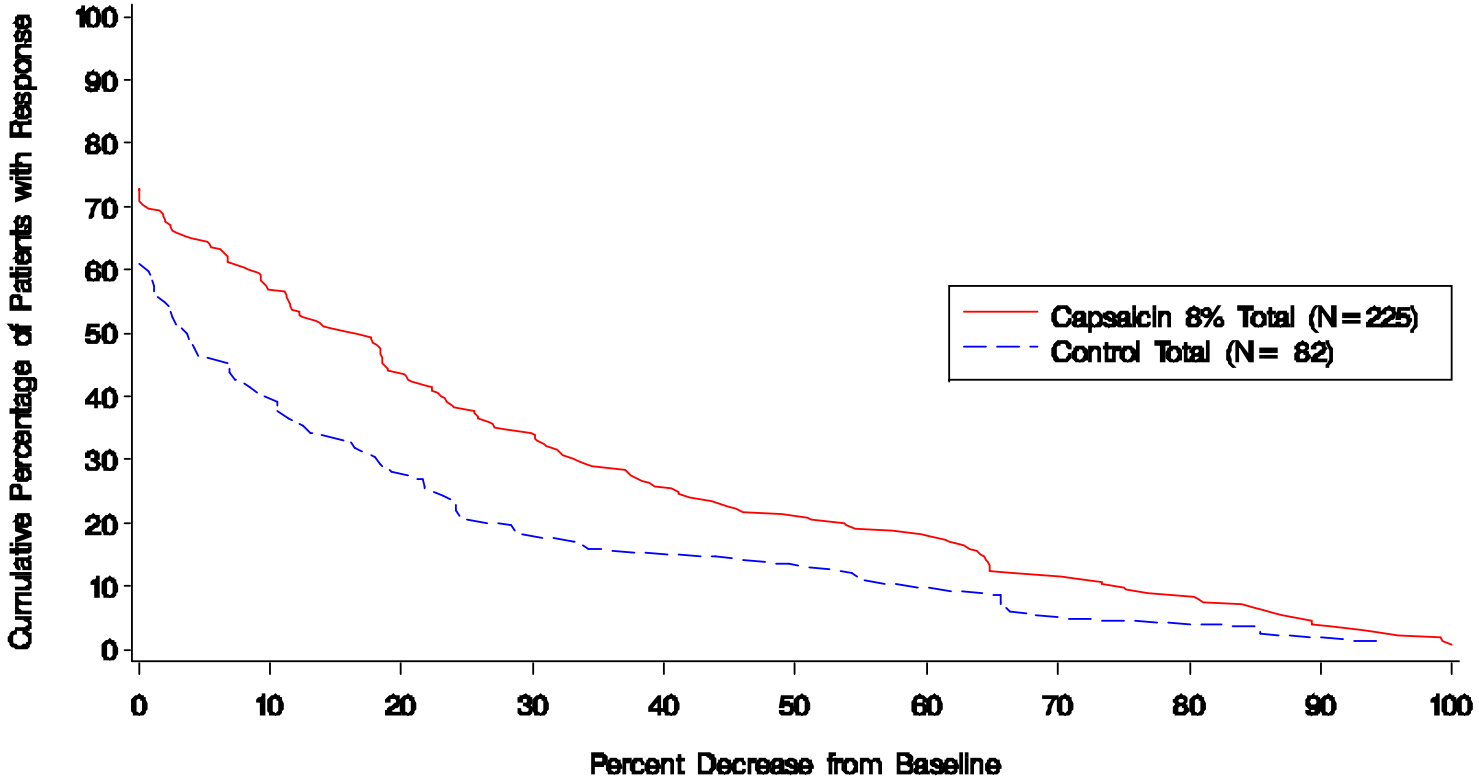
	Low-dose Control	Capsaicin 8% Patch			
	Total N = 82	30 min N = 72	60 min N = 78	90 min N = 75	Total N = 225
≥ 30% Decrease from Baseline in "Average Pain for the Past 24 Hours", n (%)	15 (18%)	30 (42%)	19 (24%)	27 (36%)	76 (34%)
p-value[a]		0.0017	0.392	0.0085	0.0093

Note: Baseline pain level was defined as the mean of all available non-biased Screening NPRS scores. Missing scores on Day 8 were estimated using the Baseline score; missing scores during Days 9 to 84 were estimated using the previous non-missing score.

[a]P-value was computed using logistic regression to test for a difference between the Capsaicin 8% Patch group and the total low-dose Control group, with Baseline pain score, pre-LMX4 pain score, and percent change in pain score after LMX4 treatment as covariates.

In Study C107, a greater proportion of subjects in the total Capsaicin 8% Patch group compared with the total low-dose Control group reported any decrease (> 0%) in pain from Baseline during Weeks 2 to 12 (71% versus 60%, respectively; Figure 3) and the proportion of subjects reporting decreases in pain was greater for the total Capsaicin 8% Patch group compared with the total low-dose Control group at all levels of response. Similarly, the 30-minute Capsaicin 8% Patch group had a greater proportion of subjects reporting any reduction (> 0%) in pain from Baseline during Weeks 2 to 12 (72% versus 60%, respectively) and a greater proportion of subjects responding at each level of response compared with the total low-dose Control group. The 90-minute Capsaicin 8% Patch group also had a greater proportion of subjects reporting any decrease in pain from Baseline during Weeks 2 to 12 (77% versus 60%, respectively).

Figure 3 **Cumulative Distribution of Mean Percent Change in NPRS Scores from Baseline during Weeks 2 to 12 -- Study C107**



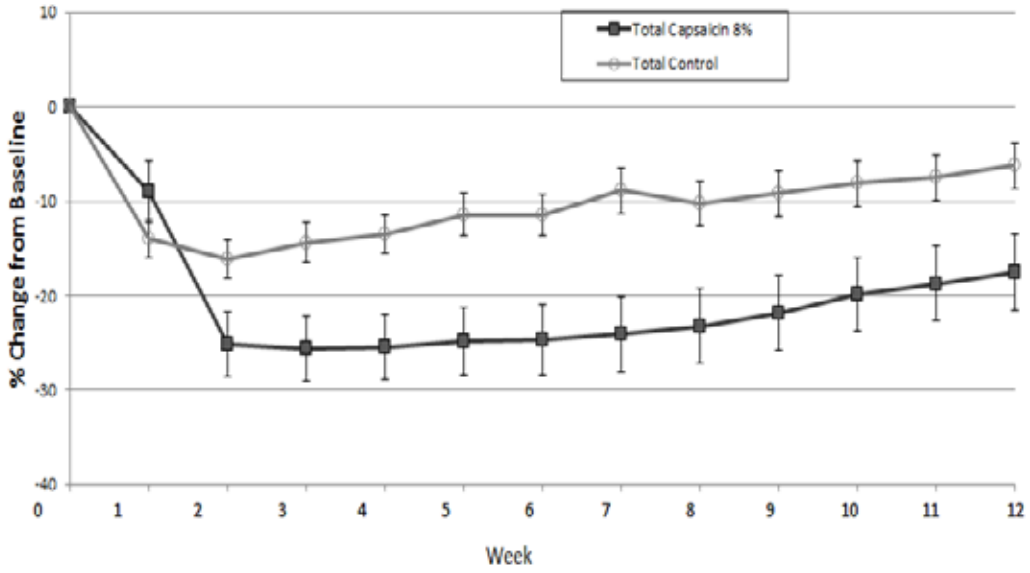
NPRS=Numeric Pain Rating Scale.

Figure 4A shows the mean percent change in "average pain for the past 24 hours" NPRS scores from Baseline by week for Study C107. The average daily pain scores during Week 1 following treatment declined compared to Baseline values, although the differences in mean NPRS scores between the total Capsaicin 8% Patch and Control groups were not statistically significant. By Week 2, subjects in the total Capsaicin 8% Patch group reported a mean percent change from Baseline in NPRS scores (i.e., less pain) of -25% compared with a mean percent change of -16% in the Control group. Subjects in the total Capsaicin 8% Patch group continued to report greater reductions in pain compared with the Control group at each subsequent week through Week 12; all weekly differences were statistically significant ($P < 0.05$) starting from Week 2. Although the rate of change in pain scores gradually lessened over time for subjects in all treatment groups, at Week 12 the total Capsaicin 8% Patch group continued to have a significantly greater mean percent change from Baseline in NPRS score of -18% ($P = 0.0187$) compared with -6.2% for the total low-dose Control group.

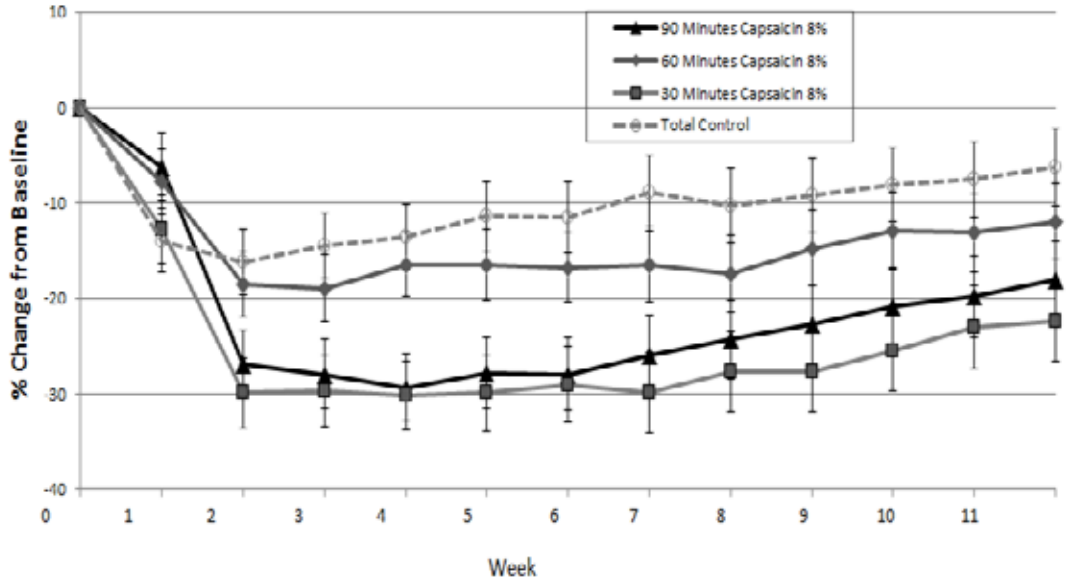
Among the individual dose groups, beginning at Week 2 and at each week through Week 12, the 30-minute Capsaicin 8% Patch group had significantly greater mean percent reductions in NPRS scores from Baseline compared with the total low-dose Control group (Figure 4B). Similarly, the 90-minute Capsaicin 8% Patch group had significantly greater mean percent reductions in NPRS scores from Baseline compared with the total low-dose Control group beginning at Week 2 and at each subsequent week through Week 12. Subjects treated with Capsaicin 8% Patch for 60 minutes showed small, consistent, but not significantly greater improvements in pain compared with the total low-dose Control beginning at Week 2 and at each subsequent week through Week 12. At Week 12, the 30-, 60-, and 90-minute Capsaicin 8% Patch group had a mean percent change from Baseline in NPRS score of -22%, -12%, and -18% ($P = 0.0098$, 0.3289, and 0.0231, respectively) compared with -6.2% for the total low-dose Control group.

Figure 4 **Weekly LS Mean Percent Change in NPRS Score from Baseline during Double-Blind Phase -- Study C107**

A.



B.



LS = least squares; NPRS=Numeric Pain Rating Scale.

Statistically significantly superior differences favoring nearly all Capsaicin 8% Patch groups were noted at Week 12 or Termination visit for the Gracely Pain Score, BPI, SFMPQ, PGIC, and CGIC (Table 5).

Table 5 Secondary Efficacy Endpoints – Study C107

	Low-dose Control	Capsaicin 8% Patch			
	Total N = 82	30 min N = 72	60 min N = 78	90 min N = 75	Total N = 225
Gracely Pain Scores: Change from Baseline to Week 12, n	68	61	64	60	185
Mean ± SD	-0.04 ± 0.32	-0.22 ± 0.54	-0.24 ± 0.45	-0.17 ± 0.41	-0.21 ± 0.47
p-value[a]	–	<0.05	<0.01	NS	<0.01
BPI: Change from Baseline to Week 12, n	67	62	64	61	187
24 hour Worst Pain (Mean ± SD)	-0.8 ± 2.1	-2.4 ± 2.8	-1.7 ± 2.6	-1.1 ± 2.7	-1.7 ± 2.7
p-value[a]	–	<0.01	<0.05	NS	<0.01
SFMPQ: Change from Baseline to Week 12					
Sensory Score, n	60	61	60	59	180
Mean ± SD	-2.1 ± 6.8	-6.7 ± 7.0	-7.2 ± 7.5	-4.8 ± 7.3	-6.2 ± 7.3
p-value[a]	–	<0.001	<0.001	<0.05	<0.001
Total Score, n	59	61	60	59	180
Mean ± SD	-3.2 ± 8.8	-9.0 ± 9.4	-9.7 ± 9.7	-6.3 ± 9.8	-8.3 ± 9.7
p-value[a]	–	<0.001	<0.001	NS	<0.001
PGIC: Week 12, n	65	62	64	61	187
Much / Very Much Improved	9 (14%)	23 (37%)	18 (28%)	20 (33%)	61 (33%)
p-value[b]	--	0.0027	0.0471	0.0119	0.0037
Slight/Much/Very Much Improved, n (%)	20 (31%)	40 (65%)	45 (70%)	40 (66%)	125 (67%)
p-value[b]	–	<0.001	<0.001	<0.05	<0.001
CGIC: Week 12, n	65	62	63	61	186
Much / Very Much Improved	9 (14%)	18 (29%)	13 (21%)	14 (23%)	45 (24%)
p-value[b]	--	0.0503	0.3544	0.2492	0.1135
Slight/Much/Very Much Improved, n (%)	24 (37%)	40 (65%)	40 (63%)	43 (70%)	123 (66%)

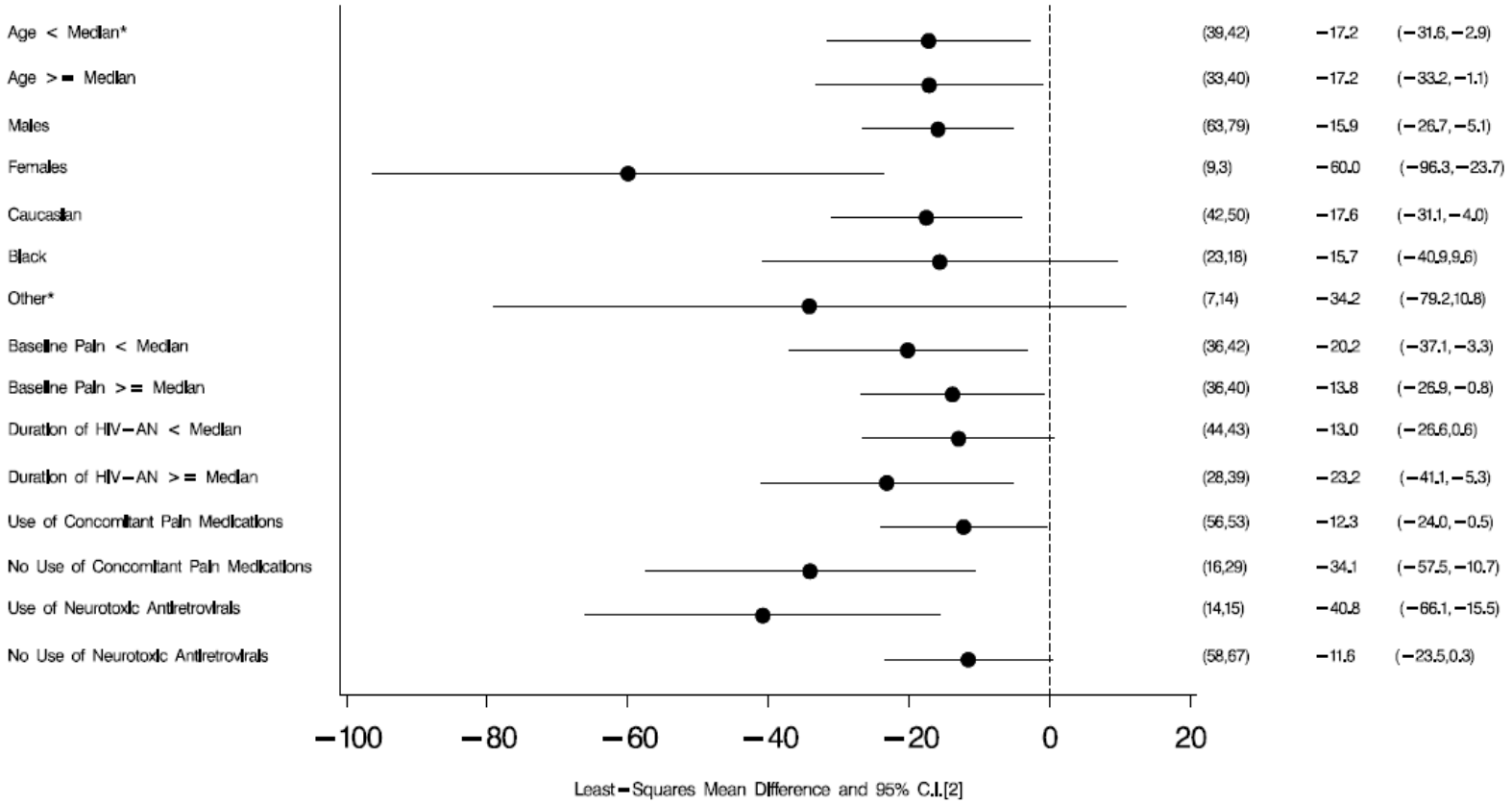
	Low-dose Control	Capsaicin 8% Patch			
	Total N = 82	30 min N = 72	60 min N = 78	90 min N = 75	Total N = 225
p-value[b]	–	<0.05	<0.05	<0.05	<0.01

BPI = Brief Pain Inventory; CGIC = Clinical Global Impression of Change; PGIC = Patient Global Impression of Change; SD = Standard deviation; SFMPQ = Short-Form McGill Pain Questionnaire.
[a]P-value was computed using the t-test comparing differences between each Capsaicin 8% Patch group and the pooled Control group.
[b]P-value was computed using the *Cochran–Mantel–Haenszel* test comparing differences in the proportion between each Capsaicin 8% Patch group and the pooled Control group.
Source: Module 5, CSR C107: Table 23

Capsaicin 8% Patch treatment for 30 minutes consistently resulted in greater improvements in NPRS scores, as assessed by mean percent change in during Weeks 2 to 12 compared to pooled low-dose Control treatments, in all subgroups regardless of gender, age, race, Baseline pain score, concomitant neuropathic pain medication use, HIV-PN duration, and neurotoxic antiretroviral use (Figure 5). Treatment differences in NPRS scores favored the 30-minute Capsaicin 8% Patch treatment regardless of gender, age, race, Baseline pain score, duration of HIV-PN, use of neurotoxic antiretroviral, and use of concomitant neuropathic pain medication.

Pain reductions in Capsaicin 8% Patch subjects treated for 30 minutes were larger in subjects not using concomitant neuropathic pain medications compared with those using concomitant neuropathic pain medications. As shown in Figure 5, subjects not using concomitant pain medication had a greater pain reduction from Baseline in Weeks 2 to 12 compared to subjects with concomitant pain medication (-34.1% versus -12.3%, respectively) when the Capsaicin 8% Patch 30-minute treatment group was compared to the low-dose Control, with overlapping 95% CI. Given that over two-thirds of subjects enrolled in this study were taking other concomitant neuropathic pain medications, the observed overall magnitude of pain reduction in this study may have underestimated the magnitude of effect that would be observed in a population with fewer subjects taking concomitant neuropathic pain medications.

Figure 5 **Percent Change in "Average Pain for the Past 24 Hours" NPRS Scores from Baseline to Weeks 2 to 12 LOCF by Subgroup Least Squares Mean Difference and 95% Confidence Intervals (Intent-to-Treat Population) – Study 107**



Note: Capsaicin 8% Patch = 640 mcg/cm2 capsaicin; Control = Capsaicin 3.2 mcg/cm2. Subjects are summarized under randomized treatment. Baseline pain level is defined as the mean of all available non-biased screening NPRS scores.

[1]N = (n of Capsaicin 8% Patch 30-minute group, n of pooled control group).

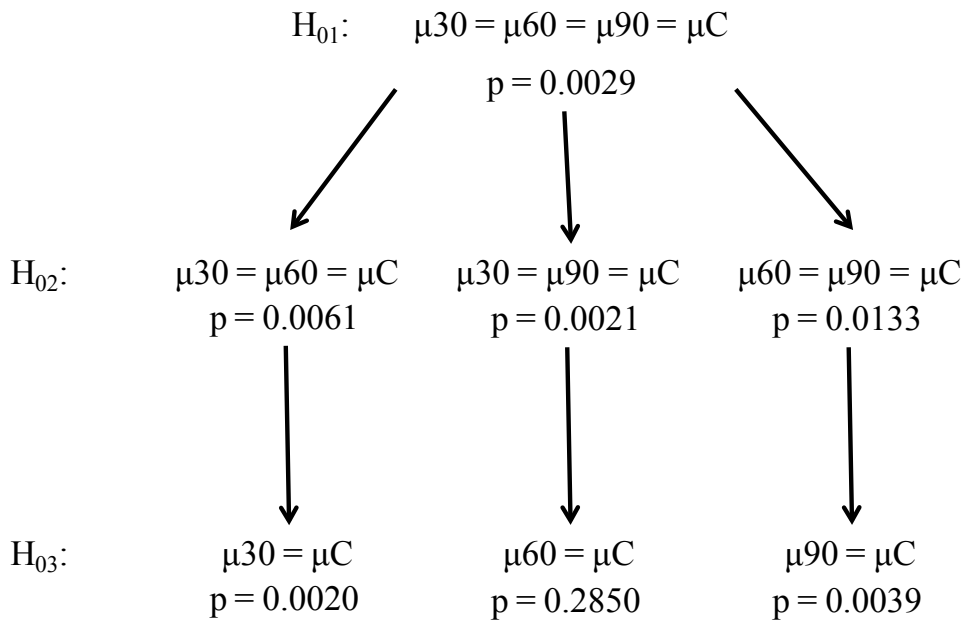
[2]For the gender subgroups, LS mean differences and 95% CIs are computed using ANCOVA to test for difference between Capsaicin 8% Patch 30-minute and pooled control groups, with baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates. For all other subgroups, LS mean differences and 95%CIs are computed using gender-stratified ANCOVA to test for difference between the Capsaicin 8% Patch 30-minute and pooled control groups with baseline pain, pre=LMX4 pain, and percent change in pain during LMX4 application as covariates.

*Due to imbalance in gender strata, the gender covariate is not used in the ANCOVA model.

4.3.4.1 Exploratory Analyses of the Primary Endpoint

A number of alternative statistical methods (i.e. sensitivity analyses) for analyzing the primary endpoints are described in Appendix E. For example, as an alternative to the gate keeping method used in the prespecified primary analysis to maintain study wide type-I error, the Bonferroni method and the Hochberg method [Hochberg 1988] were used. Moreover, the closed test procedure [Marcus 1976] demonstrated that both the 30-minute and 90-minute Capsaicin 8% Patch applications were significantly superior to the low-dose Control (P = 0.0020 and 0.0039, respectively) (Figure 6) in reducing the pain intensity score during Weeks 2 to 12.

Figure 6 **Primary Efficacy Outcome Using Closed Testing Procedure - Study C107**



In addition to the closed testing method, the conservative Bonferroni method or the Hochberg procedure demonstrated that the 30-minute dose, along with the 90-minute dose had robust evidence of efficacy. For example, the p-values for the 30-minute and 90-minute dose groups against low-dose Control were both less than 0.017 (0.05/3), the level of significance defined by the Bonferroni method. Similarly, using the Hochberg procedure to adjust for multiplicity (which sorts the p-values from high to low and calculates critical p-values for each

comparison) also leads to the conclusion that both the 30-minute and 90-minute application time groups are statistically significant in terms of the primary efficacy endpoint (Table 6).

Table 6 Hochberg Procedure: Adjustment for Multiplicity -- Study C107

Study C107 (K = 3, Number of tests)	Versus Low-dose Control (total)	Test	p-value[a]	Adjustment Factor	Critical p-value
	Capsaicin 8% Patch 60 minutes	J = 3	p-1 = 0.2910	(K-J+1)=1	0.050
	Capsaicin 8% Patch 90 minutes	J = 2	p-2 = 0.0046	(K-J+1)=2	0.025
	Capsaicin 8% Patch 30 minutes	J = 1	p-3 = 0.0007	(K-J+1)=3	0.025

ANCOVA = analysis of covariance.
[a]P-value was computed using gender stratified ANCOVA to test for a difference between the Capsaicin 8% Patch group and the total low-dose Control group, with Baseline pain score, pre LMX4 pain score, and percent change in pain score after LMX4 treatment as covariates.

Dworkin and colleagues [Dworkin 2011] have recommended that assumptions underlying the use of parametric models should be assessed and study conclusions should be examined to determine whether they depend on the method of analysis. In the presence of non-normality, the assumptions underlying parametric analyses such as the prespecified ANCOVA, consisting of normality of error terms, equality of error variances for different treatments, and/or equality of slopes for the different treatment regression lines, will no longer be valid. To address this issue, a Shapiro-Wilk test [Shapiro 1965] to evaluate normality was performed on the residuals of the primary endpoint analyses. The results demonstrated a non-normal distribution of the residuals of primary endpoint analyses data for almost all treatment groups ($P < 0.0001$); therefore, the following non parametric analyses were performed that are appropriate for situations in which the normality assumptions are not satisfied.

The results of the rank analysis of covariance (described in Appendix E), adjusting for gender and with Baseline pain, pre-LMX4 pain score, and percent change in pain score after LMX4 treatment as covariates are presented in Table 7. These results showed a significant difference between the total, 90-, and 30-minute Capsaicin 8% Patch groups and the total low-dose Control group ($P = 0.0089$, $P = 0.0027$, and $P = 0.0031$, respectively), but not between the 60-minute Capsaicin 8% Patch and the total Control group ($P = 0.36$).

The results of the stratified Wilcoxon (van Elteren 1960) test also showed a significant difference in percent change in pain from Baseline during Weeks 2 to 12 between the total, 90-, and 30-minute Capsaicin 8% Patch groups and the total Control group ($P = 0.0088$, $P = 0.0028$, and $P = 0.0025$, respectively) (Table 7). The difference in percent change in pain

from Baseline between the 60-minute Capsaicin 8% Patch group and the total Control group was not significant (P = 0.3509).

Table 7 Summary of Mean Percent Change in NPRS Scores from Baseline during Weeks 2 to 12 -- Study C107

	Control	Capsaicin 8% Patch			
	Total	30 min	60 min	90 min	Total
N	82	72	78	75	225
Baseline, mean (SE)	5.9 (0.2)	5.9 (0.2)	5.8 (0.2)	6.1 (0.2)	5.9 (0.1)
LS Mean % Change (SE)	-10.6 (3.4)	-27.7 (3.6)	-15.8 (3.4)	-24.6 (3.5)	-22.8 (2.0)
Treatment difference [a] (95% CI)		-17.0 (-27, -7.2)	-5.1 (-15, 4.4)	-14.0 (-24, -4.3)	-12.2 (-20, -4.3)
p-value [b]		0.0007	0.2885	0.0046	0.0024
p-value [c]		0.0031	0.3547	0.0027	0.0089
p-value [d]		0.0025	0.3509	0.0028	0.0088

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; NPRS = Numeric Pain Rating Scale; SE = standard error.

[a]Treatment difference was the difference of the LS Mean between Capsaicin 8% Patch and the total Control group using gender-stratified ANCOVA, with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates.

[b]P-value was computed using gender-stratified ANCOVA to test for differences between Capsaicin 8% Patch and the total Control group, with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates.

[c]P-value was computed using rank ANCOVA through the Cochran-Mantel-Haenszel test procedure to detect the difference between Capsaicin 8% Patch and the total Control group while controlling for gender and patch duration (for comparison between total groups only), with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates.

[d]P-value was computed using a stratified Wilcoxon (van Elteren 1960) test to test for differences between Capsaicin 8% Patch groups and the total Control group, with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates. For comparisons between the total Capsaicin 8% Patch and the total Control groups, the test was stratified by gender and duration. For comparisons between each individual Capsaicin 8% Patch group and the total Control group), the test was stratified by gender.

These results demonstrate the robustness of the study results and confirm that, independent of the analyses methods used (parametric or nonparametric), the 90-minute and 30-minute Capsaicin 8% Patch treatments provided significant pain relief compared with the low-dose Control in Study C107.

4.3.5 Repeat Dosing Experience in Open-Label Extension Phase

4.3.5.1 Time to First Re-Treatment

Subjects were eligible to enter a 40-week open-label extension in Study C107 following the 12 week double-blind phase, in which they could receive up to three additional and sequential 60-minute Capsaicin 8% Patch treatments, administered a minimum of 12 weeks apart, at Weeks 12, 18, 24, 30, 36, and/or 42. Subjects remained blinded to the treatment that they received during the double-blind phase while they participated in the open-label phase of Study C107.

Subjects were encouraged to remain in the study for follow-up even if they did not wish to receive open-label treatment, and to complete daily pain diaries and attend all study required follow up visits. Therefore, evaluating the time to the first open-label retreatment was used as a measure of the duration of effect of the initial double-blind treatment beyond Week 12.

Out of the 307 subjects in the double-blind phase of Study C107, 285 subjects participated in the re-treatment extension study. A summary of time to first retreatment for Study C107 is presented in Table 8. For this analysis, 42 subjects discontinued prior to Day 81 (3 days window for Week 12) and were excluded. The data are shown graphically in Figure 7 for the 30-minute Capsaicin 8% Patch group and the total low-dose Control group.

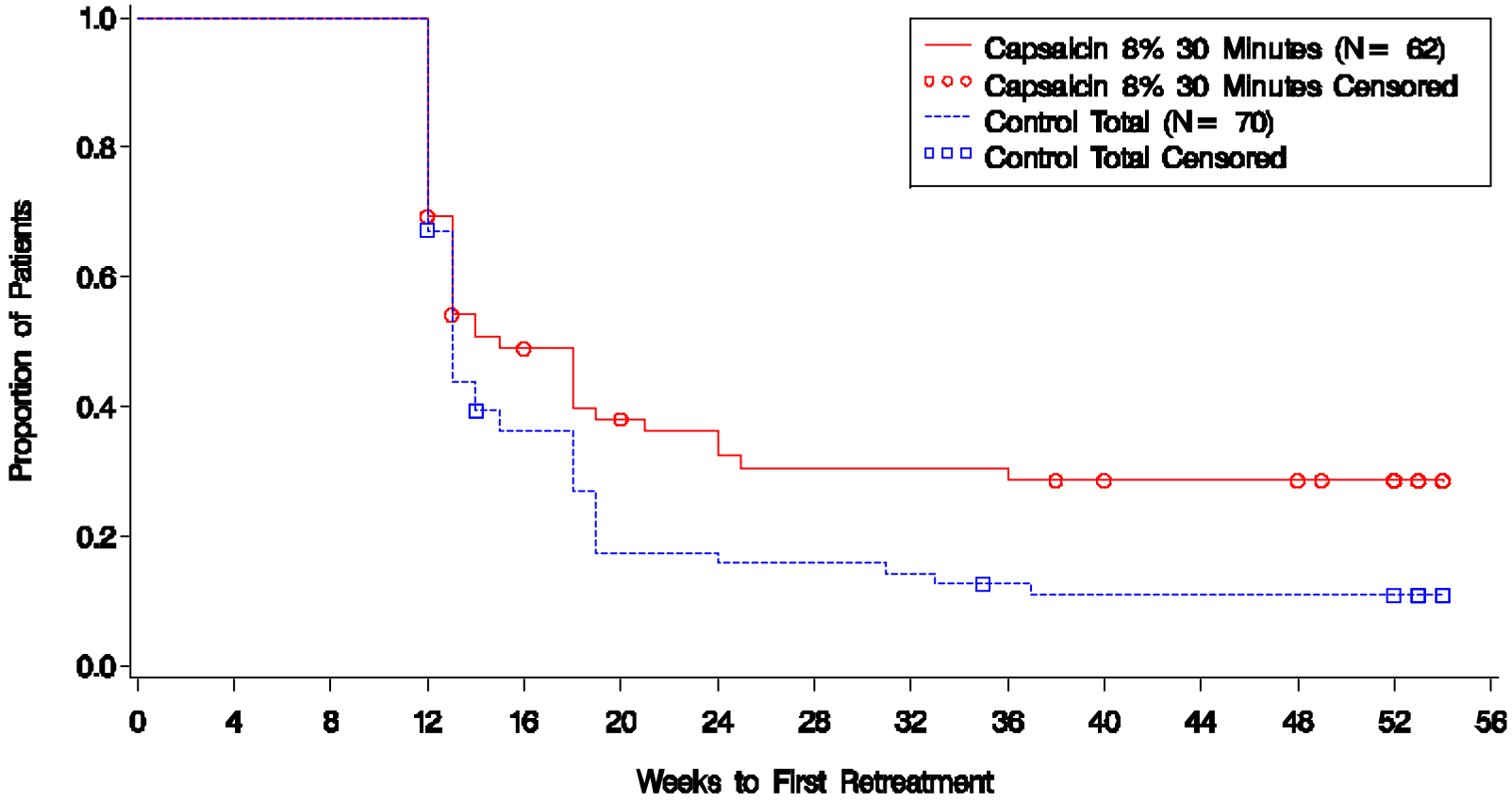
The median time to first treatment for the total Capsaicin 8% Patch group was 18 weeks compared with 13 weeks for the total low-dose Control group, with duration difference between the 2 groups being significant (P = 0.0022). Of additional note is that the subjects were not allowed to receive a retreatment until Week 12. Among the individual dose groups, the median time to first treatment for the 30-, 60-, and 90-minute Capsaicin 8% Patch group was 15, 18, and 18 weeks, respectively, all of which were significantly longer compared to the low-dose Control group (range of P-values: 0.0027 – 0.0327).

Table 8 Summary of Time to First Retreatment in Weeks – Study C107

	Low-dose Control	Capsaicin 8% Patch			
	Total	**30 min**	**60 min**	**90 min**	**Total**
Subjects who received retreatment, n	60	42	47	42	131
Censored subjects, n	10	20	21	23	64
1st Quartile (25% retreatment), mean	12.0	12.0	12.0	13.0	12.0
Median (50% retreatment), mean	13.0	15.0	18.0	18.0	18.0
3rd Quartile (75% retreatment), mean	19.0	N/A	36.0	N/A	N/A
95% CI of median	13.00, 15.00	13.00, 21.00	13.00, 25.00	14.00, 30.00	13.00, 19.00
p-value[a]		0.0327	0.0291	0.0027	0.0022

CI = confidence interval, N/A = not available.
[a]P-value was computed using Log Rank Test to test for differences between Capsaicin 8% Patch and the total low-dose Control group.

Figure 7 **Time to First Retreatment for the 30-minute Capsaicin 8% Patch Group versus Total Low-dose Control Group – Study C107**



4.3.5.2 Effectiveness of Repeated Treatment

Table 9 shows the mean percent change in NPRS scores from Baseline during Weeks 2 to 12 of the final treatment administered by the total number of Capsaicin 8% Patch treatments received during the study. Subjects receiving a single Capsaicin 8% Patch treatment during the study had a mean percent decrease from Baseline of -26%. Subjects receiving 2 or more Capsaicin 8% Patch treatments demonstrated similar decreases from Baseline ranging from -23% to -27%, indicating that the response to treatment is reproducible.

Table 9 Summary of NPRS Scores from Baseline during Weeks 2 to 12 after the Final Treatment by Number of Capsaicin 8% Patch Treatments Received – Study C107

	Total Number of Capsaicin 8% Patch Treatments			
	1 N = 118	2 N = 57	3 N = 50	4 N = 28
NPRS Score:				
Baseline, mean (SE)	5.8 (0.2)	5.7 (0.2)	6.2 (0.3)	5.6 (0.3)
% Change, mean (SE)	-25.8 (3.1)	-27.1 (4.9)	-24.6 (5.3)	-22.7 (7.0)
Proportion of Responders:				
≥30% Decrease from Baseline, n (%)	45 (38%)	26 (46%)	18 (36%)	9 (32%)

NPRS = Numeric Pain Rating Scale, SE = standard error.

Note: Baseline pain level was defined as the mean of all available non-biased Screening NPRS scores in that category. If the last treatment was during the double-blind phase, then missing scores on Day 8 were estimated using the Baseline score; missing scores during Days 9–84 were estimated using the previous non-missing score. If the last treatment was an open-label treatment, then missing scores were not imputed, and subjects with less than 39 pain scores during Weeks 2 to 12 after the last treatment were excluded.

Therefore, the data from the open-label extension phase of Study C107 indicates that the efficacy of the Capsaicin 8% Patch is reproducible and does not decrease upon retreatment, suggesting that tolerance does not develop with repeated treatments with the Capsaicin 8% Patch. Similar findings were observed in the PHN population receiving repeated Capsaicin 8% Patch treatments [Backonja 2010].

4.3.6 Summary of Study C107 Efficacy Findings

The results of this controlled double-blind study provide substantial evidence that treatment with a single application of a Capsaicin 8% Patch provides significant and clinically meaningful pain relief over 12 weeks in subjects with painful HIV-PN. When all efficacy

endpoints are considered, Capsaicin 8% Patch treatment for 30, 60, or 90 minutes resulted in a flat dose response (in terms of application time duration) with regards to pain intensity score reduction. The analgesic effect of the Capsaicin 8% Patch was observed within 1 to 2 weeks of administration and persisted for 12 weeks or longer. As the magnitude of the benefit observed following a 90-minute and 30-minute treatment were comparable, the 30-minute application duration is the recommended application duration.

An alternative hierarchical closed testing procedure, which did not assume a linear monotonic dose response, and several other statistical methods that control for multiple comparisons, including the conservative Bonferroni method (performed retrospectively), demonstrated that the 90-minute and 30-minute doses were superior to Control. The efficacy results were robust and independent of the analyses methods used (parametric or nonparametric).

The results from the open-label extension of Study C107 demonstrate that the efficacy associated with the Capsaicin 8% Patch treatment is maintained following repeated treatment over a period of 1 year with significantly longer time to the first retreatment for the Capsaicin 8% Patch group compared to the low-dose Control group (median time to re-treatment 18 versus 13 weeks).

No apparent differences in demographic characteristics were detected that could explain the decreased response in the 60-minute group (Table 1). Random variability within the individual dose groups appears to be the most plausible explanation for the smaller than expected NPRS reductions in the 60-minute group compared with the 30- and 90-minute groups. This conclusion is based, in part, on the results of multiple secondary efficacy endpoints such as the PGIC, CGIC, Gracely Pain Score, BPI, and SFMPG demonstrating that the 60-minute dose provided benefits comparable to the other doses (Table 5). Moreover, the results from 60-minute Capsaicin 8% Patch treatments administered during the open-label extension phase (Table 9) were similar to the results observed for the 30- and 90-minute Capsaicin 8% Patch treatment groups after the initial double-blind treatment.

5. Study C119 of Capsaicin 8% Patch in HIV-PN

5.1 Study C119 Design

Study C119 was a Phase 3, 12-week multicenter, randomized, double-blind, controlled study conducted to evaluate the efficacy and safety of the Capsaicin 8% Patch for the treatment of painful HIV-PN. The initial Treatment Visit generally occurred within 14-21 days after Screening. Subjects were randomized to receive a single application of the Capsaicin 8% Patch or low-dose Control patches for 30 or 60 minutes.

A 90-minute application group was not included in Study C119 based on the fact that it was found to be not superior to the 30-minute dose in Study C107.

5.1.1 Study Centers and Patient Population

A total of 480 subjects were planned for this study and 494 subjects were actually enrolled from 78 study centers in the United States (US), Canada, United Kingdom, and Australia.

Subjects could have been on stable chronic pain medication regimens but were not to be currently using any topical pain medications on the affected areas, such as non-steroidal anti-inflammatory drugs (NSAIDs), menthol, methyl salicylate, local anesthetics including Lidoderm® (5% lidocaine patch), steroids, or capsaicin products. Similar to C107, if a subject was taking any pain medications chronically at the time of the Screening Visit, subjects must have been on a stable (not p.r.n.) regimen for at least 21 days prior to the Study Patch Application Visit (Day 0) and willing to maintain these medications at the same stable doses and schedule throughout the study. This included, but was not limited to anticonvulsants, NSAIDs, oral or transdermal opioids including tramadol, and/or antidepressants including duloxetine hydrochloride but excluded selective serotonin reuptake inhibitors (SSRI's).

No p.r.n. pain medications were allowed during the trial except for short-term use of opioid-based oral pain medications, between Day 0 and Day 5, and acetaminophen (paracetamol) up to total of 3 g/day as needed for aches and pain throughout screening and study participation in addition to their stable daily dose pain regimen, if any.

5.1.2 Treatment Area Identification and Application Procedure

Similar to C107, Study C119 followed the same procedures to identify the treatment area and to apply the Capsaicin 8% Patch (see Section 4.1).

5.1.3 Primary Endpoint

The primary efficacy endpoint for Study C119 was the percent change in "average pain for past 24 hours" (i.e., the average daily pain score) in the treated area(s), as assessed by NPRS score, from Baseline to Weeks 2 to 12 (i.e., the same primary endpoint as in Study C107). Additional details of this endpoint are provided in Section 4.1.3.

5.1.4 Secondary Endpoints

The secondary efficacy endpoints included: (1) the proportion of subjects achieving a ≥30% or ≥2 units decrease in their "average pain for the past 24 hours" NPRS scores from Baseline during Weeks 2 to 12; (2) Weekly mean percent change in the "average pain for the past 24 hours" NPRS score from Baseline through Week 12, within each treatment group.

Other secondary endpoints were change from Baseline to Week 12 for PGIC, CGIC, SAT, SFMPQ, and SF-36v2™ Health Survey (SF-36v2). The details of these endpoints were provided in Section 4.1.4, except for the SF-36v2, which is a scale designed to measure a subject's views about their own health and how their health influences his or her activities.

5.2 Clinical and Statistical Methodology

5.2.1 Statistical Methods

5.2.1.1 Sample Size and Powering

For Study C119, a sample size of 480 subjects was determined based on a two-sided Student's t-test to detect a difference of 10% change in NPRS scores from Baseline between the combined Capsaicin 8% Patch group and the combined low-dose Control group, with a standard deviation of 31%, at a 0.05 significance level with over 90% power. Subjects were randomized in a 2:2:1:1 allocation scheme (Capsaicin 8% Patch for 60 and 30 minutes and Control patch for 60 and 30 minutes) with the Capsaicin 8% Patch containing capsaicin 640 µg/cm^2 and the low-dose Control patch containing 3.2 µg/cm^2 (0.04%) capsaicin.

5.2.1.2 Analysis Populations

All efficacy parameters were assessed in the Intent-to-Treat (ITT) population. The details are provided in Section 4.2.1.2.

For Study C119, the ITT population was modified as two subjects were inadvertently enrolled twice in the study. For these subjects, only efficacy data collected prior to the date of the second treatment were used for all analyses.

5.2.1.3 Primary Statistical Analysis

Calculation of Baseline Score

For Study C119, the Baseline average pain intensity score was the average of all NPRS scores from Day -14 through Day -1.

Prespecified Primary Endpoint Analysis

The primary statistical null hypothesis was H_o: "There is no difference between the average of control and average of active (Capsaicin 8% Patch) from 30- and 60-minute groups in the percent change in the 'average pain for the past 24 hours' NPRS scores" from Baseline to Weeks 2 to 12. The hypothesis was to be tested at an a level of 0.05. As this was the primary hypothesis of this study, a rejection of the null hypothesis (H_o) would provide statistical evidence of the efficacy of the Capsaicin 8% Patch compared to the low-dose Control.

Treatment differences were to be compared by a gender stratified ANCOVA model with Baseline pain score as a covariate performed on the modified Intent-to-Treat population. The covariate adjusted treatment differences, D_m and D_f, were first calculated for male subjects and female subjects, respectively. Then, the overall sample size weighted treatment difference, D, was calculated as $D = w_m D_m + w_f D_f$, where $w_m = n_m /n$ and $w_f = n_f /n$. The sample size for each strata was n_m and n_f, for male and female subjects, respectively, and the total sample size of the modified Intent-to-Treat population was represented as $n = n_m + n_f$.

If the null hypothesis for the primary analysis was rejected, comparison of each Capsaicin 8% Patch dose group versus the control group was to be performed to assess the treatment effect. Before such comparisons, the poolability of the 30- and 60-minute low-dose Control groups was assessed by the 90% confidence interval (CI) approach proposed by Westlake [Westlake 1976]. If the 90% CI fell within the equivalence margin, determined by the 80% to 125% ratio of the

means of the 60- and 30-minute groups using the approach outlined in the Center for Drug Evaluation and Research guidance for bioequivalence [US FDA CDER 2001], then the results from the two low-dose Control groups were to be pooled and each individual Capsaicin 8% Patch group was to be compared with the pooled low-dose Control group.

If the two low-dose Control groups could not be pooled, then each individual Capsaicin 8% Patch group was to be compared with their respective low-dose Control group using a gender-stratified ANCOVA model with the Baseline pain score as the only covariate.

5.2.1.4 Handling of Missing NPRS Scores

The handling of missing data was identical with Study C107. The detailed descriptions are provided in Section 4.2.1.4.

5.2.2 Methods for Secondary Endpoints

For proportion of responders (i.e., subjects who achieved ≥ 30% decrease in mean "average pain for the past 24 hours" NPRS score from Baseline) during Weeks 2 to 12, treatment differences were compared by using the gender-stratified logistic regression with the Baseline pain score. In addition, the odds ratio of observing responses in the Capsaicin 8% Patch group compared with the low-dose Control group, and its 95% CI, were estimated.

Weekly mean percent changes in the "average pain for the past 24 hours" NPRS score from Baseline through Week 12 were plotted for each week and compared among each treatment groups.

Each Capsaicin 8% Patch group was compared to the respective low-dose Control group for change from Baseline to Week 12 using Fisher's exact test for PGIC and CGIC, Cochran-Mantel-Haenszel for SAT, and gender-stratified ANCOVA, with the Screening score as the covariate, for SF-36v2™.

5.3 Clinical Efficacy

5.3.1 Demographic and Other Baseline Characteristics

Table 10 shows demographic and other baseline characteristics of subjects in Study C119. The demographic and other baseline characteristics of subjects in the Capsaicin 8% Patch group (n = 332) were similar to the low-dose Control group (n = 162).

The average age of subjects enrolled in Study C119 was 50 years. The majority of subjects were Caucasian and male. The average Baseline pain level, as measured by NPRS score, ranged from 5.9 to 6.2. Most subjects in both treatment groups had a treatment area >750 cm^2. At Baseline, 7.5% of Capsaicin 8% Patch subjects and 5% of low-dose Control subjects were using neurotoxic antiretrovirals.

The average duration of HIV-PN was 6.3 years in the Capsaicin 8% Patch group and 5.8 years in the low-dose Control group. Most subjects (69% of Capsaicin 8% Patch and 66% of low-dose Control subjects) were using some form of concomitant neuropathic pain treatments at Baseline.

Table 10 Baseline Characteristics – Study C119

Characteristic	Low-dose Control			Capsaicin 8% Patch		
	30 min N = 73	60 min N = 89	Total N = 162	30 min N = 167	60 min N = 165	Total N = 332
Mean Age in years (SD)	49.2 (7.8)	50.2 (9.4)	49.7 (8.7)	50.5 (8.3)	49.0 (8.5)	49.7 (8.5)
Gender, n (%)						
Male	64 (88)	78 (88)	142 (88)	142 (85)	148 (90)	290 (87)
Race, n (%)						
Black	17 (23)	22 (25)	39 (24)	40 (24)	43 (26)	83 (25)
Caucasian	50 (69)	57 (64)	107 (66)	114 (68)	113 (69)	227 (68)
Other[a]	6 (8.2)	10 (11)	16 (9.9)	13 (7.8)	9 (5.5)	22 (6.6)
Treatment Area, n (%)						
≤ 250 cm^2	1 (1)	2 (2)	3 (2)	2 (1)	3 (2)	5 (2)
$> 250 - \leq 500$ cm^2	8 (11)	8 (9)	16 (10)	13 (8)	13 (8)	26 (8)
$> 500 - \leq 750$ cm^2	17 (23)	11 (12)	28 (17)	27 (16)	31 (19)	58 (18)
> 750 cm^2	47 (64)	68 (76)	115 (71)	125 (75)	118 (72)	243 (73)
Mean Duration of Pain in years (SD)	6.2 (4)	5.5 (5)	5.8 (4)	6.2 (4)	6.4 (4)	6.3 (4)
Mean Baseline Pain Level (SD)[b]	5.9 (2)	5.9 (2)	5.9 (2)	6.0 (2)	6.2 (2)	6.1 (2)
On Concomitant Pain Medication[c], n (%)	53 (73)	54 (61)	107 (66)	124 (74)	106 (64)	230 (69)
Using Neurotoxic Antiretrovirals[d], n (%)	2 (3)	6 (7)	8 (5)	11 (7)	14 (9)	25 (8)
CD4 (x10^6/L), n	69	83	152	156	155	311
Mean	497.8	463.4	479.0	443.0	403.9	423.5
SD	302	350	329	220	252	237
HIV RNA (copies/mL)[e], n	62	81	143	148	149	297
Mean	6994.2	16490.5	12373.2	9460.8	25976.4	17746.4
SD	23690	59200	47310	58800	81530	714980
Median	400.0	400.0	400.0	400.0	400.0	400.0

[a]Other includes subjects who classified themselves as Asian or as Other.
[b]Baseline pain level was defined as the mean of all available NPRS scores from Day -14 to Day -1.
[c]Subjects were defined as being on concomitant pain medication if he or she was on an anticonvulsant, non- selective serotonin reuptake inhibitor antidepressant or opioid that was issued on Day -1 and was taken for a total duration of at least 7 consecutive days.
[d]Subjects were defined as using neurotoxic antiretrovirals if he or she was on neurotoxic antiretrovirals, such as Didanosine, Stavudine, or Zalcitabine, for at least eight weeks prior to the Screening date.
[e]For HIV RNA, values reported as "< 400" were replaced with the numeric value 400 and values reported as "< 40" were replaced with the numeric value 40.

5.3.2 Disposition

The disposition of subjects participating in controlled Study C119 is presented in Table 11. Overall, 93% and 94% of Capsaicin 8% Patch and low-dose Control subjects, respectively, completed the 12-week, double-blind study. Two subjects withdrew due to an AE: a 60-minute Capsaicin 8% Patch subject on Day 16 with worsening of hepatitis C and cholecystitis and a low-dose Control subject following a fall-related injury during the Screening period. One (<1%) subject in the Capsaicin 8% Patch group died during the 12-week double-blind study. The cause of death was atherosclerotic vascular disease and this was not considered to be related to study treatment.

Table 11 Subject Disposition: Controlled HIV-PN – Study C119

Characteristic	Low-dose Control			Capsaicin 8% Patch		
	30 min N = 73	60 min N = 89	Total N = 162	30 min N = 167	60 min N = 165	Total N = 332
Subjects Completed n (%)	71 (97)	81 (91)	152 (94)	156 (93)	153 (93)	309 (93)
Subject Withdrawal Due to:						
Adverse Event n (%)	0	1 (1)	1 (< 1)	0	1 (< 1)	1 (< 1)
Unsatisfactory Response n (%)	0	1 (1)	2 (2)	0	1 (< 1)	1 (< 1)
Non-Compliance n (%)	0	2 (2)	2 (1)	1 (< 1)	1 (< 1)	2 (< 1)
Lost to Follow-Up n (%)	2 (3)	0	2 (1)	3 (2)	2 (1)	5 (2)
Death n (%)	0	0	0	0	1 (< 1)	1 (< 1)
Other n (%)	0	4 (5)	4 (3)	7 (4)	6 (4)	13 (4)

5.3.3 Primary Efficacy Endpoint

The total Capsaicin 8% Patch group reported numerically larger pain reductions than the low-dose Control group (-30% versus -25%, respectively; P = 0.0967) (Table 12). Therefore, the pain reduction observed in Study C119 failed to meet the prespecified statistical criterion to establish superiority of the Capsaicin 8% Patch against the low-dose Control group. The Study C119 results appeared to be confounded by a larger than anticipated analgesic response in the 60-minute low-dose Control group and a large difference in pain reduction between the 60- and 30-minute low-dose Control groups (-30% versus -19%; Table 12).

Because the ratio of means between the 60- and 30-minute low-dose Control groups was 1.57 (90% CI: 1.12, 2.35), which is greater than the prespecified efficacy equivalence margin ratio of 80% to 125%, the 60- and 30-minute low-dose Control groups were not pooled for the testing of the individual dose groups. As a result, each Capsaicin 8% Patch dose group was compared in exploratory analyses, with their respective low-dose Control group instead of with the total low-dose Control group (thus reducing the sample size and thereby reducing the power to detect a treatment difference of 10% from 82% to 65%).

Nonetheless, although the primary endpoint of the study was not met based on the prespecified statistical criterion, an effect favoring the 30-minute Capsaicin 8% Patch group was observed in the primary prespecified analysis (P = 0.1031), with a 7.1% treatment difference favoring the 30-minute Capsaicin 8% Patch group over the 30-minute low-dose Control group.

Table 12 Percent Change in NPRS Scores from Baseline during Weeks 2 to 12 – Study C119

	Low-dose Control			Capsaicin 8% Patch		
	30 min	60 min	Total	30 min	60 min	Total
NPRS Score	N = 73	N = 89	N = 162	N = 167	N = 165	N = 332
Baseline						
Mean (SE)	5.9 (0.2)	5.9 (0.2)	5.9 (0.1)	6.0 (0.1)	6.2 (0.1)	6.1 (0.08)
% Change from Baseline						
LS Mean (SE)	-19.1 (3.6)	-30.0 (3.3)	-24.5 (2.4)	-26.2 (2.4)	-32.8 (2.4)	-29.5 (1.7)
95% CI of LS Mean	-26.2, -12.0	-36.5, -23.7	-29.4, -19.8	-30.8, -21.4	-37.5, -28.01	-32.8, -26.1
p-value[a]	–	–	–	0.1031	0.4884	0.0967

ANCOVA = analysis of covariance, LS = Least Squares, NPRS = Numeric Pain Rating Scale, SE = standard error.
Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day-14 through Day -1, inclusive. Missing scores on or before Day 8 were estimated using the Baseline score; missing scores after Day 8 were estimated using the previous non-missing score. If all post-treatment NPRS scores were missing, then Baseline score was used for imputation.
[a]P-value was computed using gender-stratified ANCOVA to compare differences between the Capsaicin 8% Patch group and the respective low-dose Control group, with Baseline pain score as the covariate.

As an exploratory analysis using the same ANCOVA model as prespecified, the dose response was tested as the prespecified primary analysis with the inclusion of treatment (Capsaicin 8% Patch versus low-dose Control) by patch duration (30 and 60 minutes) assessing the interaction effect in the model. This interaction was not statistically significant with P = 0.525, supporting the conclusion of homogeneity of the differences between the respective doses and their

corresponding controls. Thus, all doses evaluated were on the plateau portion of the dose response curve; i.e., there is a flat dose response (a similar result to the same analysis performed in Study C107).

The magnitude of the missing data is low. For Study C119, amongst the 461 (93%) subjects who completed the study, only 88 (19%) subjects missed reporting an NPRS score for at least a day and, out of these, 53 (11%) subjects missed reporting an NPRS score for two days and 25 (6%) subjects missed reporting an NPRS score for 3 or more days. Due to its low frequency, missing data did not impact the outcome of the primary endpoint.

5.3.4 Secondary Efficacy Endpoints

The proportion of subjects responding to treatment (i.e., ≥30% pain reduction) was larger in magnitude for the 30-minute Capsaicin 8% Patch group (39%) compared with the 30-minute low-dose Control group (26%). However, the between group difference was P = 0.0553 and therefore did not meet the prespecified statistical significance level of P < 0.05 (Table 13).

Table 13 Proportion of Responders during Weeks 2 to 12 – Study C119

	Low-dose Control			Capsaicin 8% Patch		
	30 min	60 min	Total	30 min	60 min	Total
	N = 73	N = 89	N = 162	N = 167	N = 165	N = 332
≥30% Decrease from Baseline in "Average Pain for Past 24 Hours", n (%)	19 (26%)	40 (45%)	59 (36%)	65 (39%)	79 (48%)	144 (43%)
p-value[a]	–	–	–	0.0553	0.5582	0.0662

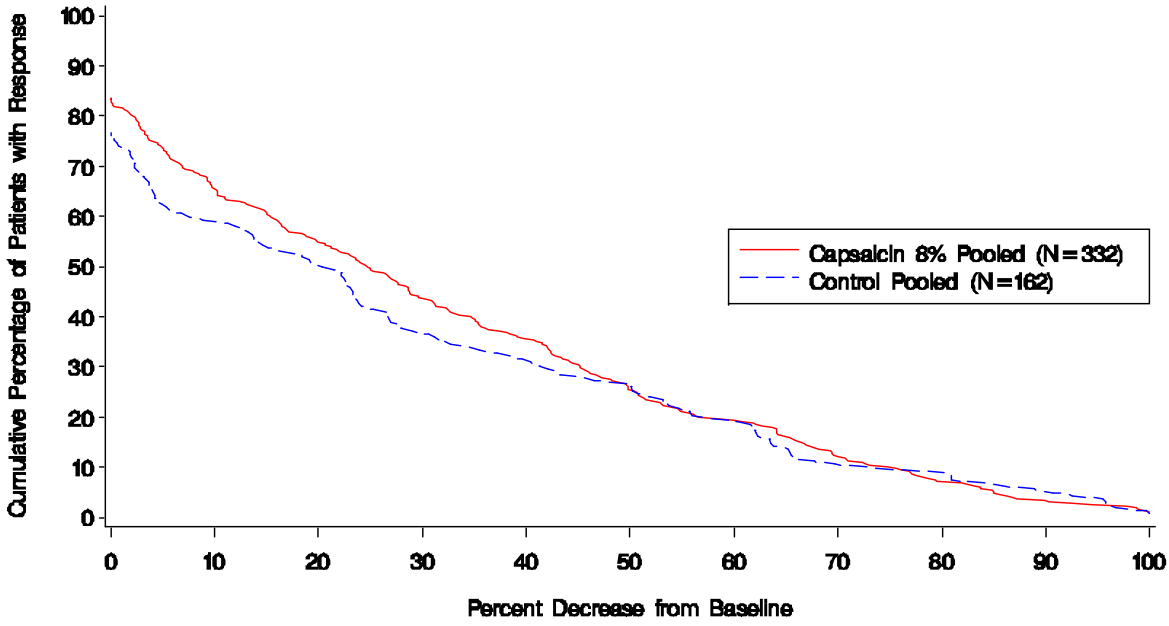
Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day-14 through Day-1, inclusive. Missing scores on or before Day 8 were estimated using the Baseline score; missing scores after Day 8 were estimated using the previous non-missing score. If all post-treatment NPRS scores were missing, then Baseline score was used for imputation.

[a]P-value was computed using logistic regression to compare differences between each Capsaicin 8% Patch group and the respective patch application time low-dose Control group, with Baseline pain and gender as the covariates.

In Study C119, a greater proportion of subjects in the total Capsaicin 8% Patch group compared with the total Control group reported a decrease (>0%) in pain from Baseline during Weeks 2 to 12 (83% versus 75%, respectively; Figure 8) and the proportion of subjects reporting a decrease in pain was greater for the total Capsaicin 8% Patch group compared with the total Control group at response levels up through ³ 40%; above that level, no differences were observed. Similarly, the 30-minute Capsaicin 8% Patch group had a greater proportion of subjects reporting a reduction in pain from Baseline during Weeks 2 to 12 compared with the

30-minute Control group (81% versus 69%, respectively) and the proportion of subjects reporting a decrease in pain was greater for the 30-minute Capsaicin 8% Patch group compared with the 30-minute Control group at response levels up through ³ 40% (Figure 8); above that level, no differences were observed. The differences in the proportion of subjects responding between the 60-minute Capsaicin 8% Patch group and the 60-minute Control group were smaller than for the 30-minute dose but favored the Capsaicin 8% Patch group at response levels up through ³ 40%, and a greater proportion of subjects in the 60-minute Capsaicin 8% Patch group compared with the 60-minute Control group reported any decrease (>0%) in pain from Baseline during Weeks 2 to 12 (84% versus 81%, respectively).

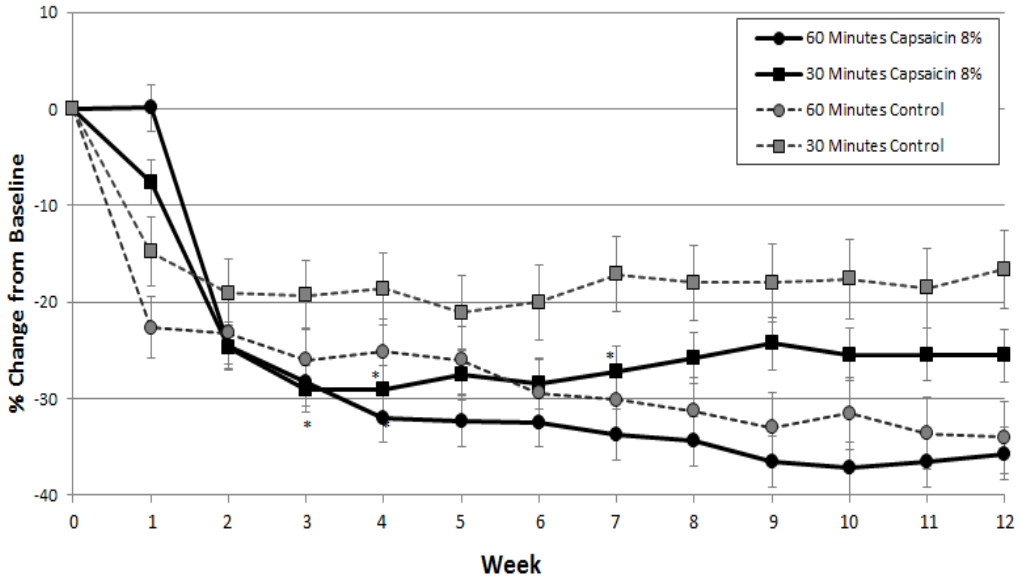
Figure 8 **Cumulative Distribution of Mean Percent Change in NPRS Scores from Baseline during Weeks 2 to 12 – Study C119**



During Week 1 following treatment, subjects in the total Capsaicin 8% Patch group reported a smaller mean percent change in NPRS scores from Baseline compared with the total Control group (-3.7% versus -19%). This finding is likely related to the transient increase in pain associated with the application of Capsaicin 8% Patch in subjects with HIV-PN. After Week 1, subjects in the total Capsaicin 8% Patch group reported greater, though not significant, reductions in NPRS scores compared with the total Control group during Week 2 and at every subsequent week of the 12-week study.

Although the differences were relatively small, greater reductions compared with Control in weekly mean percent change from Baseline were observed in the 60-minute Capsaicin 8% Patch group beginning at Week 3 and continuing through Week 12 (Figure 9). At Week 12, the total Capsaicin 8% Patch group had a mean percent change from Baseline in NPRS score of -31% compared with -25% for the total Control group (P = 0.121) and the 30-minute Capsaicin 8% Patch group had a mean percent change from Baseline in NPRS score of -26% (P = 0.0736) compared with -17% for the 30-minute Control.

Figure 9 **Weekly LS Mean Percent Change in NPRS Score from Baseline – Study C119**



LS = least squares, NPRS=Numeric Pain Rating Scale.

The results of other secondary endpoint analyses in Study C119 provide additional support for the efficacy of Capsaicin 8% Patch in subjects with HIV-PN (Table 14). At Week 12/Termination, a significantly greater proportion of Capsaicin 8% Patch-treated subjects reported improvement ("very much," "much," or "slightly" improved) on the PGIC in the total and 30-minute groups compared with the respective low-dose Control groups (67% versus 55%, P = 0.0106 for the total group and 65% versus 45%, P = 0.0057 for the 30-minute group). Results of the CGIC were consistent with those of the PGIC. Differences in PGIC or CGIC in the 60-minute treatment groups were not significant. On the SAT questionnaire, a greater proportion of subjects in the 30-minute Capsaicin 8% Patch group compared with the 30-minute low-dose Control group indicated an improvement ("somewhat/much better") in pain level (62% and 41%, respectively), activity level (44% and 26%, respectively), and "quality of life" (50% and 30%, respectively) after treatment (all P < 0.01). No significant differences on the SAT were observed between the 60-minute treatment groups. The 30-minute Capsaicin 8% Patch group showed greater improvements in mean SF-36v2 scores compared with their respective low-dose Control group in all categories. Statistical significance was demonstrated for mean Physical Functioning (9.0 versus -1.7, respectively; P < 0.0001), Role Physical (11.5 versus 3.5, respectively; P = 0.0189), and Social Functioning (11.0 versus 1.3,

respectively; P = 0.0022). The differences between the 60-minute Capsaicin 8% Patch and low-dose Control groups were minimal.

Table 14 Secondary Efficacy Endpoints – Study C119

	Low-dose Control			Capsaicin 8% Patch		
	30 min N = 73	**60 min N = 89**	**Total N = 162**	**30 min N = 167**	**60 min N = 165**	**Total N = 332**
PGIC: Week 12, n	71	81	152	158	154	312
Slight/Much/Very Much Improved, n (%)	32 (45%)	51 (63%)	83 (55%)	103 (65%)	106 (69%)	209 (67%)
p-value[a]	–	–	–	0.0057	0.3843	0.0106
CGIC: Week 12, n	71	81	152	158	153	311
Slight/Much/Very Much Improved, n (%)	28 (39%)	51 (63%)	79 (52%)	103 (65%)	101 (66%)	204 (66%)
p-value[a]	–	–	–	0.0003	0.6674	0.0060
SAT: Week 12, n	70	81	151	157	153	310
Pain Level Better	29 (41%)	49 (61%)	78 (52%)	98 (62%)	95 (62%)	193 (62%)
Pain Level Worse	13 (19%)	8 (9.9%)	21 (134%)	16 (10%)	6 (3.9%)	22 (7.1%)
p-value[b]	–	–	–	0.0082	0.7149	0.0385
Activity Level Better	18 (26%)	42 (52%)	60 (40%)	69 (44%)	66 (43%)	135 (44%)
Activity Level Worse	13 (19%)	6 (7.4%)	19 (13%)	10 (6.4%)	8 (5.2%)	18 (5.8%)
p-value[b]				0.0014	0.4209	0.1367
Quality of Life Better	21 (30%)	41 (51%)	62 (41%)	79 (50%)	72 (47%)	151 (49%)
Quality of Life Worse	14 (20%)	4 (4.9%)	18 (12%)	8 (5.1%)	3 (2.0%)	11 (3.5%)
p-value[b]	–	–	–	0.0006	0.8169	0.0275

	Low-dose Control			Capsaicin 8% Patch		
	30 min N = 73	60 min N = 89	Total N = 162	30 min N = 167	60 min N = 165	Total N = 332
SF-36v2™: Week 12						
Physical Functioning, n	70	80	150	155	152	307
LS Mean (SE)	1.7 ± 2	6.9 ± 2	2.6 ± 2	9.0 ± 2	9.9 ± 2	9.5 ± 1
p-value[c]	–	–	–	<0.0001	0.2483	0.0003
Role physical, n	71	81	152	154	152	306
LS Mean (SE)	3.5 ± 3	13 ± 3	8.1 ± 2	12 ± 2	12 ± 2	12 ± 1
p-value[c]	–	–	–	0.0189	0.9126	0.1042
Bodily Pain, n	71	81	152	156	154	310
LS Mean (SE)	5.6 ± 2	12 ± 2	8.7 ± 2	11 ± 2	14 ± 2	12 ± 1
p-value[c]	–	–	–	0.0631	0.5021	0.0704
General Health, n	70	79	149	156	153	309
LS Mean (SE)	2.0 ± 2	1.7 ± 2	0.1 ± 1	1.3 ± 1	2.0 ± 1	1.7 ± 0.9
p-value[c]	–	–	–	0.1439	0.8929	0.2496
SF-36v2™: Week 12						
Vitality, n	69	80	149	156	153	309
LS Mean (SE)	0.4 ± 2	9.4 ± 2	4.5 ± 1	3.5 ± 1	6.3 ± 1	4.9 ± 0.9
p-value[c]	–	–	–	0.1029	0.1681	0.8156
Social Functioning, n	70	81	151	156	154	310
LS Mean (SE)	1.3 ± 3	10.6 ± 2	6.0 ± 2	11.0 ± 2	6.8 ± 2	8.9 ± 1
p-value[c]	–	–	–	0.0022	0.1998	0.1811
Role Emotional, n	71	81	152	154	154	308
LS Mean (SE)	2.6 ± 3	13 ± 3	7.9 ± 2	7.8 ± 2	8.4 ± 2	8.1 ± 2
p-value[c]	–	–	–	0.1386	0.1553	0.9300
Mental Health, n	71	81	152	155	150	305
LS Mean (SE)	0.9 ± 2	4.1 ± 2	2.5 ± 1	1.3 ± 1	2.6 ± 1	1.9 ± 0.9
p-value[c]	–	–	–	0.8612	0.5100	0.7406

ANCOVA = analysis of covariance, CGIC = Clinical Global Impression of Change, LS Mean = least squares mean, PGIC = Patient Global Impression of Change, SAT = Self-Assessment of Treatment, SD = standard deviation, SE = standard error, SF-36v2 = Short Form-36 version 2 Health Survey.

[a]P-value was computed from Fisher's exact test comparing each Capsaicin 8% Patch group and the respective low-dose Control group.

[b]P-value was computed from Cochran-Mantel-Haenszel test comparing each Capsaicin 8% Patch group and the respective low-dose Control group.

[c]P-value was computed using gender-stratified ANCOVA to test for differences between each Capsaicin 8% Patch group and the respective low-dose Control group, with the Screening score as the covariate.

5.3.5 Exploratory Analyses of the Primary Endpoint

A number of alternative statistical methods (i.e. sensitivity analyses) for analyzing the primary endpoints are described in Appendix E. For example, the ANCOVA model used in the pivotal Study C107 was also applied to Study C119 to compare results of the primary endpoint analyses across both Phase 3 studies. This approach was selected because covariate analyses of Study C119 and the integrated data had demonstrated that the pre-topical anesthetic (pre-LMX4) pain and change in pain following topical anesthetic application were significant covariates. Treatment differences were thus compared in Study C119 using a gender-stratified ANCOVA model with Baseline pain score, pre-LMX4 pain score, and percent change in pain score after LMX4 treatment as covariates.

In Study C119, using the same gender-stratified ANCOVA model as C107, a significantly greater reduction in mean percent change in NPRS scores from Baseline during Weeks 2 to 12 was demonstrated in the total Capsaicin 8% Patch treatment group compared with the total Control group (-30% versus -24%, P = 0.0413) with a treatment difference of -5.9% (95% CI: -11.6, -0.2) (Table 15). Among the individual dose groups, subjects treated with Capsaicin 8% Patch for 30 minutes had a numerically larger reduction in mean percent change in NPRS scores compared with the 30-minute Control group (-27% versus -19%, P = 0.0572) resulting in a treatment difference of -8.0% (95% CI: -16.3, 0.2). Although a numerically greater reduction in mean percent change in NPRS scores from Baseline was seen following treatment with Capsaicin 8% Patch for 60 minutes compared with the respective Control group (treatment difference of -3.8%; 95% CI: -11.6, 4.0), this difference was not statistically significant.

Table 15 Summary of Mean Percent Change in NPRS Scores from Baseline during Weeks 2 to 12 -- Study C119

	Low-dose Control			Capsaicin 8% Patch		
	30 min	60 min	Total	30 min	60 min	Total
N	73	89	162	167	165	332
Baseline, mean (SE)	5.9 (0.2)	5.9 (0.2)	5.9 (0.1)	6.0 (0.1)	6.2 (0.1)	6.1 (0.1)
LS Mean % Change (SE)	-18.5 (3.5)	-29.2 (3.2)	-23.9 (2.4)	-26.6 (2.3)	-33.0 (2.3)	-29.8 (1.6)
Treatment difference[a] (95% CI)				-8.0 (-16, 0.2)	-3.8 (-12, 4.0)	-5.9 (-12, -0.2)
p-value[b]				0.0572	0.3368	0.0413
p-value[c]				0.0251	0.2061	0.0147
p-value[d]				0.0353	0.4331	0.0442

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; NPRS = Numeric Pain Rating Scale; SE = standard error.

[a]Treatment difference was the difference of the LS Mean between Capsaicin 8% Patch and the respective Control group using gender-stratified ANCOVA, with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates.

[b]P-value was computed using gender-stratified ANCOVA to test for differences between Capsaicin 8% Patch and the respective Control group, with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates.

[c]P-value was computed using rank ANCOVA through the Cochran-Mantel-Haenszel test procedure to detect the difference between Capsaicin 8% Patch and the respective Control group while controlling for gender, with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates.

[d]P-value was computed using a stratified Wilcoxon (van Elteren 1960) test to test for differences between Capsaicin 8% Patch groups and the respective Control group, with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates. For comparisons between the total Capsaicin 8% Patch and the total Control groups, the test was stratified by gender and duration. For comparisons between each Capsaicin 8% Patch application time group and its respective low-dose Control group, the test was stratified by gender.

Similar to Study C107, a Shapiro–Wilk test [Shapiro 1965] to detect normality was performed retrospectively on residuals of the primary endpoint analyses from the primary ANCOVA model based on the recommendations from Dworkin and colleagues [Dworkin 2011]. As with Study C107, the Study C119 results demonstrated a non-normal distribution of the residuals of the primary endpoint analyses data ($P < 0.0001$ for all treatment groups). Therefore, the ANCOVA analysis was followed up with two nonparametric analyses (Details in Appendix E), which are appropriate for situations in which the normality assumptions are not satisfied.

The results of the rank analysis of covariance, adjusting for gender and with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as a covariate, showed a significant ($P = 0.0147$) difference between the total Capsaicin 8% Patch and Control groups

and also between the 30-minute Capsaicin 8% Patch and the 30-minute control group (P = 0.0251; Table 15).

The results of the stratified Wilcoxon (van Elteren 1960) test (stratified by gender and patch duration) also showed (Table 15) a significant difference in percent change in pain from Baseline during Weeks 2 to 12 between the total Capsaicin 8% Patch group and the total Control group (P = 0.0442; Table 15) and between the 30-minute Capsaicin 8% Patch group and the 30-minute Control (P = 0.0353).

5.3.6 Summary of Study C119 Efficacy Findings

The results from Study C119, based on totality of the data, provide evidence that treatment with a single application of Capsaicin 8% Patch for 30 minutes produces meaningful pain relief over 12 weeks in subjects with painful HIV-PN. A result favoring the 30-minute Capsaicin 8% Patch group was observed in the primary prespecified analysis (P = 0.1031). Although this result did not reach the prespecified level of statistical significance, the individual group comparisons in Study C119 were limited by the sample size of the Control arms, which resulted in lower than planned power.

Results of the PGIC and CGIC analyses did demonstrate a nominally statistically significantly superior benefit for the total Capsaicin 8% Patch and 30-minute Capsaicin 8% Patch treatment groups in Study C119. Also, all results of the SF-36v2 and SAT questionnaires numerically favored Capsaicin 8% Patch with several analyses demonstrating a significant benefit associated with the total and the 30-minute Capsaicin 8% Patch dose groups.

The exploratory nonparametric analyses showed a significant difference between the Total Capsaicin 8% Patch and the 30-minute Capsaicin 8% Patch groups and their respective Control groups. Exploratory analyses of the primary endpoint using the same ANCOVA model that was used for the primary analysis of Study C107, showed a significant difference between the Total Capsaicin 8% Patch and the 30-minute Capsaicin 8% Patch groups and their respective low-dose Control groups.

These results re-affirm the evidence that treatment with a single application of Capsaicin 8% Patch for 30 minutes produces meaningful pain relief over 12 weeks in subjects with painful HIV-PN. In conclusion, although the results from Study C119 did not provide statistically significant evidence of clinical efficacy based on the prespecified primary endpoint analysis,

the totality of the data does provide evidence of efficacy of the 30-minute Capsaicin 8% Patch application in the treatment of neuropathic pain associated with HIV-PN.

6. Integrated Analyses of Efficacy for Studies C107 and C119

6.1 Rationale for Integrated Analyses

In order to provide a robust assessment of the efficacy and safety data from the controlled Phase 3 Studies (i.e., C107 and C119), the subject level data from these studies were pooled. Studies C107 and C119 were similarly designed had similar entry criteria, the same primary endpoints and comparable demographics. In addition, a consistent effect of the Capsaicin 8% Patch was observed in all treatment arms of both studies.

Some differences were observed in the subject populations between the C107 and C119 studies, such as number of years with pain (approximately 4.8 versus 6.1 years, respectively) and percentage of subjects using neurotoxic antiretroviral drugs (18% versus 6.5%, respectively). However, these differences were considered to be unlikely to impact the efficacy or safety results of the integrated analysis.

Therefore, subject level efficacy and safety data from Studies C107 and C119 in the 30- and 60-minute active and low-dose Control arms were pooled. Efficacy data from the 90-minute active and Control arms of Study C107 were not pooled in the integrated analyses because a 90-minute Capsaicin 8% Patch application was not investigated in Study C119.

6.2 Statistical Methods

6.2.1 Analysis Populations

All analyses were based on the Intent-to-Treat (ITT) populations from both studies. The ITT population includes all randomized subjects who receive any study patch application and had at least 3 days of non-missing "average pain for the past 24 hours" NPRS scores for the calculation of Baseline average score.

6.2.2 Primary Endpoint

The primary endpoint was assessed through the daily NPRS score recorded in a diary every evening. As in Studies C107 and C119, the primary endpoint of the integrated data analysis was the percent change in "average pain for past 24 hours" NPRS score from Baseline to Weeks 2 to 12. Baseline and post baseline averages from individual studies were used to calculate the primary endpoint.

6.2.2.1 Prespecified Primary Endpoint Analyses

Treatment differences between the Capsaicin 8% Patch groups and their respective low-dose Control groups were compared using a gender-stratified ANCOVA model with Baseline pain score, pre-LMX4 pain score, and percent change in pain score after LMX4 treatment as covariates. This approach was selected because covariate analyses of the integrated data had demonstrated that the pre-LMX4 pain and change in pain following topical anesthetic application were significant covariates. Study was not used as a covariate for this analysis. Least squares (LS) mean treatment differences and 95% CIs were also calculated.

In addition, nonparametric tests (i.e., rank ANCOVA and the stratified Wilcoxon (van Elteren 1960) method, were also applied to the integrated data.

6.2.2.2 Secondary endpoints and analyses

The following secondary endpoints were analyzed in the integrated dataset:

1. Proportion of subjects with a ≥30% decrease in "average pain for past 24 hours" NPRS score from baseline to Weeks 2 to 12
2. Cumulative distribution of mean percent change in "average pain for past 24 hours" NPRS scores from Baseline during Weeks 2 to 12
3. Patient Global Impression of Change at Week 12
4. Weekly percent change from baseline in "average pain for past 24 hours" NPRS scores

The analyses methods were similar to those used in Study C107 as provided in Section 4.2.2.

6.2.2.3 Handling of Missing NPRS Scores

Missing data was handled with the modified LOCF approach described in Section 4.2.1.4.

6.3 Integrated Analyses of Efficacy for Studies C107 and C119

6.3.1 Disposition

Subject disposition for the integrated analyses of efficacy for Studies C107 and C119 is summarized in Table 16.

Overall, 92% and 91% of Capsaicin 8% Patch and low-dose Control subjects, respectively, completed the 12-week, double-blind studies. Five subjects (Capsaicin 8% Patch: n=3, <1%; low-dose Control: n=2, <1%) withdrew due to an adverse event (AE), including 2 subjects who withdrew due to treatment-related application site pain. Two (<1%) subjects in Capsaicin 8% Patch group and 2 (<1%) subjects in the low-dose Control group died during the 12-week double-blind studies and there was no relationship to study treatments.

Table 16 Subject Disposition: Controlled HIV-PN Studies C107 and C119 of Capsaicin 8% Patch

Study Drug and Duration	Low-Dose Control				Capsaicin 8% Patch			
	30 min N = 100	60 min N = 115	90 min N = 29	Total N = 244	30 min N = 239	60 min N = 243	90 min N = 75	Total N = 557
Subjects Entered	100	115	29	244	239	243	75	557
Subjects Completed, n (%)	92 (92)	105 (91)	26 (90)	223 (91)	221 (92)	223 (92)	66 (88)	510 (92)
Subject Withdrawal Due to:								
Adverse Event, n (%)	1 (1)	1 (<1)	0 (0)	2 (<1)	0 (0)	3 (1)	0 (0)	3 (<1)
Unsatisfactory Response, n (%)	1 (1)	2 (2)	0 (0)	3 (1)	0 (0)	1 (<1)	1 (1)	2 (<1)
Non-Compliance, n (%)	0 (0)	2 (2)	0 (0)	2 (<1)	1 (<1)	1 (<1)	1 (1)	3 (<1)
Lost to Follow-Up, n (%)	4 (4)	0	2 (7)	6 (2)	9 (4)	6 (2)	5 (7)	20 (4)
Death, n (%)	0 (0)	1 (<1)	1 (3)	2 (<1)	0 (0)	2 (<1)	0 (0)	2 (<1)
Other, n (%)	2 (2)	4 (3)	0 (0)	6 (2)	8 (3)	7 (3)	2 (3)	17 (3)

6.3.2 Primary Endpoint Analyses

A summary of mean percent changes in NPRS scores from Baseline during Weeks 2 to 12 in the integrated dataset is presented in Table 17.

These analyses demonstrate that the pooled Capsaicin 8% Patch treatment was significantly superior to the pooled low-dose Control (-27% versus -20%; P = 0.0034), resulting in a treatment difference of -7.4% (95% CI: -12, -2.4). The Capsaicin 8% Patch treatment for 30 minutes was significantly superior to the 30-minute low-dose Control (-27% versus -16%;

P = 0.0024), resulting in a treatment difference of -11% (95% CI: -18, -4.0). Although the 30-and 60-minute application times provided comparable pain reductions during Weeks 2 to 12 (-27% and -28%, respectively), the difference between the 60-minute Capsaicin 8% Patch groups and 60-minute low-dose Control groups was not statistically significant.

The results of the nonparametric rank ANCOVA analyses, using Baseline pain, pre-LMX4 pain score, and percent change in pain score after LMX4 treatment as covariates, showed a significant difference between the total and 30-minute Capsaicin 8% Patch groups and the respective low-dose Control groups (P = 0.0048 and P = 0.0016, respectively). Similarly, the results of the nonparametric stratified Wilcoxon [van Elteren 1960] test also showed a significantly greater reduction in mean percent change in NPRS scores from Baseline during Weeks 2 to 12 in the total Capsaicin 8% Patch (P = 0.0058) and 30-minute Capsaicin 8% Patch (P = 0.0008) treatment groups compared with their respective low-dose Control groups (Table 17). No significant difference was observed for the 60-minute groups with either test. These results using non-parametric methods established the robustness of the efficacy findings for the Capsaicin 8% Patch 30-minute application group.

In the combined dataset of the C107 and C119 studies, among subjects who completed the study, only 19% of subjects missed reporting a NPRS score for a day, 10% of subjects missed reporting a NPRS score for two days and <5% of subjects missed reporting a NPRS score for 3 or more days. This relatively small amount of missing data did not impact the outcome of the primary endpoint.

Table 17 Mean Percent Changes in NPRS Scores from Baseline during Weeks 2 to 12 and to Week 12 – Integrated Dataset

	Low-dose Control			Capsaicin 8% Patch		
	30 min	60 min	Total[a]	30 min	60 min	Total[a]
N	100	115	215	239	243	482
Baseline, mean (SE)	6.0 (0.1)	5.8 (0.1)	5.9 (0.1)	6.0 (0.1)	6.0 (0.1)	6.0 (0.1)
LS Mean % Change (SE)	-15.8 (3.1)	-24.2 (2.9)	-20.0 (2.1)	-26.9 (2.0)	-27.9 (2.0)	-27.4 (1.4)
95% CI of LS Mean	-21.8, -9.8	-29.8, -18.6	-24.1, -15.9	-30.8, -23.0	-31.7, -24.0	-30.1, -24.7
Treatment difference[b] (95% CI)				-11.1 (-18.3, -4.0)	-3.6 (-10.5, 3.2)	-7.4 (-12.3, -2.4)
p-value[c]				0.0024	0.2935	0.0034
p-value[d]				0.0016	0.3599	0.0048
p-value[e]				0.0008	0.5220	0.0058

ANCOVA = analysis of covariance, CI = confidence interval, LS = least squares, NPRS = Numeric Pain Rating Scale, SE = standard error.

[a]The "Total" group contains only those subjects treated for 30 or 60 minutes in Study C107 and all subjects in Study C119.

[b]Treatment difference was the difference of the LS Mean between Capsaicin 8% Patch and the respective low-dose Control group using gender-stratified ANCOVA, with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates.

[c]P-value was computed using gender-stratified ANCOVA to test for differences between Capsaicin 8% Patch and each respective low-dose Control group, with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates.

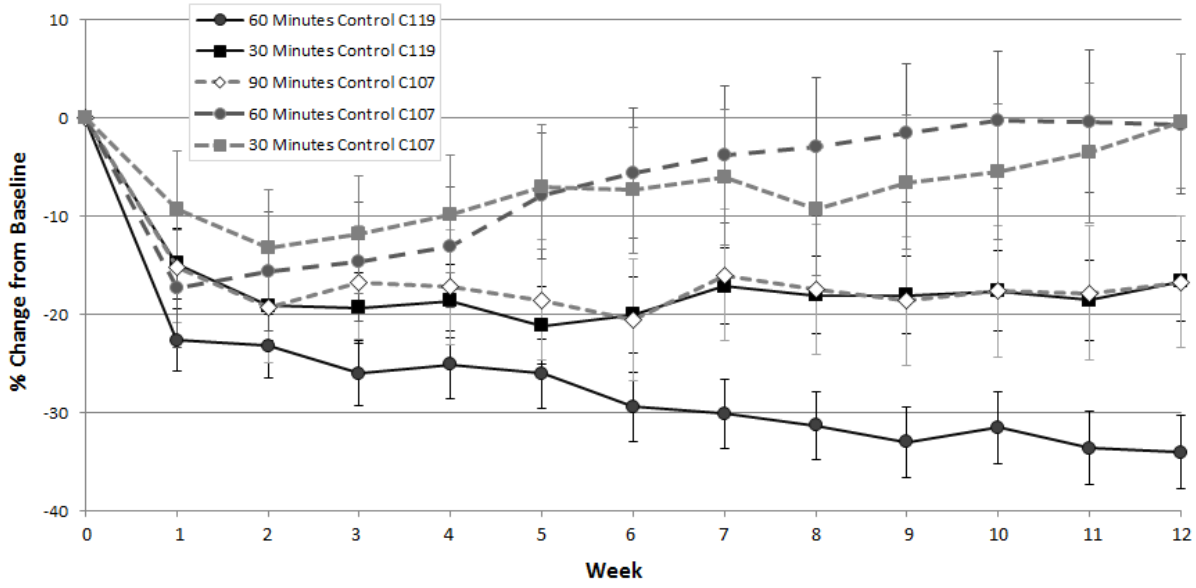
[d]P-value was computed using rank ANCOVA through the Cochran-Mantel-Haenszel test procedure to detect the difference between Capsaicin 8% Patch and the total low-dose Control group while controlling for gender and patch duration (for comparison between total groups only), with Baseline pain, pre LMX4 pain, and percent change in pain during LMX4 application as covariates.

[e]P-value was computed using a stratified Wilcoxon [van Elteren 1960] test to test for differences between Capsaicin 8% Patch groups and the total low-dose Control group, with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates. For comparisons between the total Capsaicin 8% Patch and the total low-dose Control group, the test was stratified by gender and duration. For comparisons between each individual Capsaicin 8% Patch and the total low-dose Control group, the test was stratified by gender.

A summary of the data in the low-dose-Control arms across Studies C107 and C119 is presented in Figure 10. In study C107, both the 30-minute and 60-minute application time groups had a similar pattern of response in terms of the reported pain reductions during Weeks 2 to 12. Both groups had a gradual return to Baseline values during this time period. However, a slightly different pattern was observed in the 90-minute group from Study C107 compared to the 30-minute group in Study C119 (i.e., where a stable reduction in pain scores compared to Baseline was observed from Weeks 2 to 12). By contrast, the 60-minute application time group from Study C119 exhibited a unique pattern in which pain score reduction increased from Weeks 2 to 12. Of note is the fact that this pattern was not observed in any other

Capsaicin 8% Patch group or low-dose Control group. Moreover, this pattern of progressive pain reduction over a period of many weeks following a single 60-minute application of a low-dose Control patch cannot be explained by the known molecular actions of capsaicin. In terms of the observed efficacy signal, this anomalous analgesic response pattern had a major negative impact on the statistical analysis of Study C119. However, this same analysis also indicates that there was no detectable application time related dose response to the low-dose Control patch in Studies C107 and C119.

Figure 10 **Summary of Data from Low-dose Control Arms across Studies C107 and C119**



6.3.3 Secondary Endpoint Analyses

The integrated analyses of multiple secondary endpoints demonstrate that the Capsaicin 8% Patch applied for 30 minutes is superior to the 30-minute low-dose Control treatment. For example, the proportion of responders in the Capsaicin 8% Patch applied for 30 minutes is greater than the proportion of responders in the 30-minute low-dose control treatment (i.e. 40% versus 23%, respectively; P = 0.0040; Table 18). Subjects treated with the Capsaicin 8% Patch for 30 minutes had 2.2-fold higher odds of responding compared with the 30-minute Control group. Comparable proportions of responders during Weeks 2 to 12 were observed in the 30- and 60-minute Capsaicin 8% Patch groups (40% and 40%, respectively; Table 18);

although only the proportion of responders in the 30-minute Capsaicin 8% Patch group was significantly greater than in the Control group.

Table 18 Summary of Proportion of Responders during Weeks 2 to 12

	Control			Capsaicin 8% Patch		
	30 min	**60 min**	**Total[a]**	**30 min**	**60 min**	**Total[a]**
N	100	115	215	239	243	482
³ 30% Response	23 (23)	43 (37)	66 (31)	95 (40)	98 (40)	193 (40)
Odds Ratio[b]				2.210	1.224	1.645
95% CI of Odds Ratio				1.288, 3.791	0.768, 1.950	1.151, 2.349
p-value[b]				0.0040	0.3949	0.0062

CI = confidence interval.
[a]The "Total" group contains only those subjects treated for 30 or 60 minutes in Study C107 and all subjects in Study C119.
[b]Computed using logistic regression to test for differences between Capsaicin 8% Patch and each respective Control group, with gender, Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates.

In the integrated dataset, a greater proportion of subjects in the 30-minute Capsaicin 8% Patch group compared with the 30-minute Control group reported any magnitude of decrease (>0%) in pain from Baseline during Weeks 2 to 12 (78% versus 65%), and the proportion of subjects reporting a decrease in pain was greater for the Capsaicin 8% Patch group compared with the Control group at all response levels (Figure 11). Fewer subjects in the 30-minute Capsaicin 8% Patch group compared with the 30-minute Control group reported an increase in pain from Baseline (18% versus 29%, respectively). A significant difference in the distribution of responses was observed between the total and the 30-minute Capsaicin 8% Patch group and the respective Control group (P = 0.0097 and 0.0053, respectively based on the Kolmogrov and Smirnov test), but not between the 60-minute Capsaicin 8% Patch group and the 60-minute Control group. The cumulative distribution of mean percent change in NPRS scores from Baseline during Weeks 2 to 12 for the integrated dataset is presented in Figure 11.

A summary of the change in PGIC responses at Week 12, or at termination visit, for the integrated dataset is presented in Table 19. At Week 12/Termination, the distribution of responses in the total Capsaicin 8% Patch group was significantly different from the total Control group (P = 0.0010; Table 19).

The distribution of responses in the 30-minute Capsaicin 8% Patch group was also significantly different from the 30-minute Control group (P = 0.0004). A greater proportion of

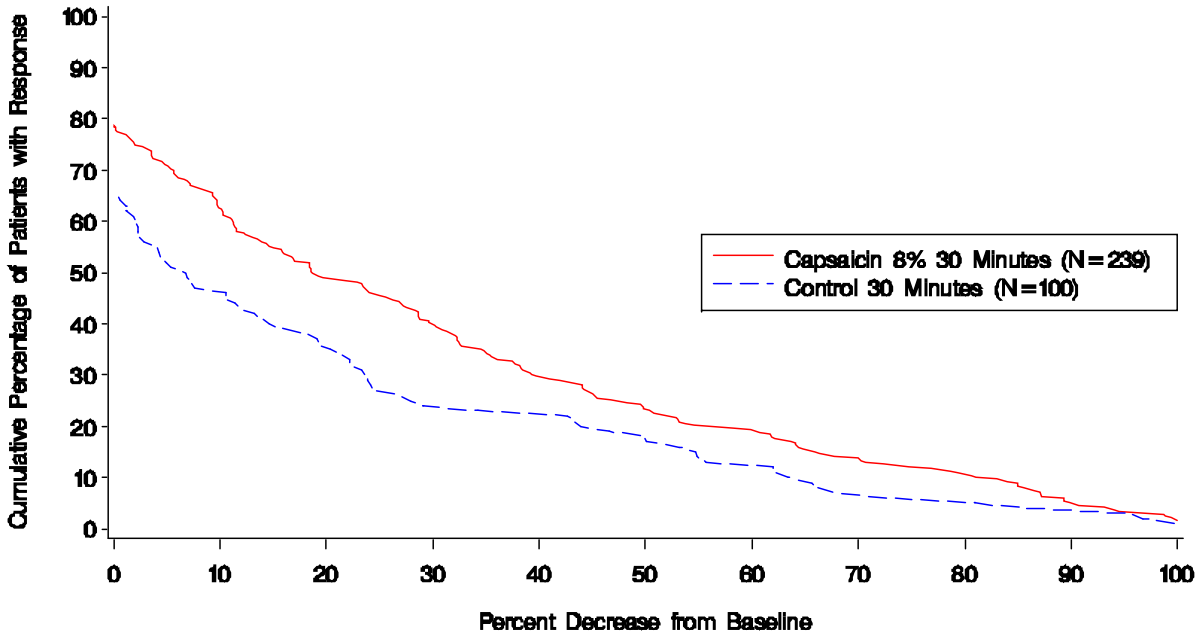
subjects in the 30-minute Capsaicin 8% Patch group compared with the 30-minute Control group felt very much improved (18% versus 11%), much improved (18% versus 11%), or slightly improved (29% versus 20%). A smaller proportion of subjects in the 30-minute Capsaicin 8% Patch group reported no change (25%) compared with 30-minute Control group (42%). Fewer subjects in the 30-minute Capsaicin 8% Patch group compared with the 30-minute Control group indicated they felt slightly worse (7.7% versus 8.7%), much worse (2.3% versus 5.4%), or very much worse (0% versus 2.2%). Although the distribution of responses between the 30- and 60-minute Capsaicin 8% Patch group was comparable, the difference in the distribution of responses was only significant compared with Control in the 30-minute treatment group.

Table 19 Summary of Patient's Global Impression of Change Analysis at Week 12

	Control			Capsaicin 8% Patch		
	30 min	**60 min**	**Total[a]**	**30 min**	**60 min**	**Total[a]**
N	92	104	196	220	218	438
Very Much Improved, n (%)	10 (11)	21 (20)	31 (16)	39 (18)	34 (16)	73 (17)
Much Improved, n (%)	10 (11)	15 (14)	25 (13)	40 (18)	45 (21)	85 (19)
Slightly Improved, n (%)	18 (20)	23 (22)	41 (21)	64 (29)	72 (33)	136 (31)
No Change, n (%)	39 (42)	36 (35)	75 (38)	55 (25)	61 (28)	116 (27)
Slightly Worse, n (%)	8 (9)	7 (7)	15 (8)	17 (8)	5 (2)	22 (5)
Much Worse, n (%)	5 (5)	2 (2)	7 (4)	5 (2)	0	5 (1)
Very Much Worse, n (%)	2 (2)	0	2 (1)	0	1 (0.5)	1 (0.2)
p-value[b]				0.0004	0.2446	0.0010

[a]The "Total" group contains only those subjects treated for 30 or 60 minutes in Study C107 and all subjects in Study C119.
[b]P-value was computed from the Cochran-Armitage trend test comparing each Capsaicin 8% Patch group against the respective Control group.

Figure 11 **Cumulative Distribution of Mean Percent Change in NPRS Scores from Baseline during Weeks 2 to 12, Integrated Dataset**

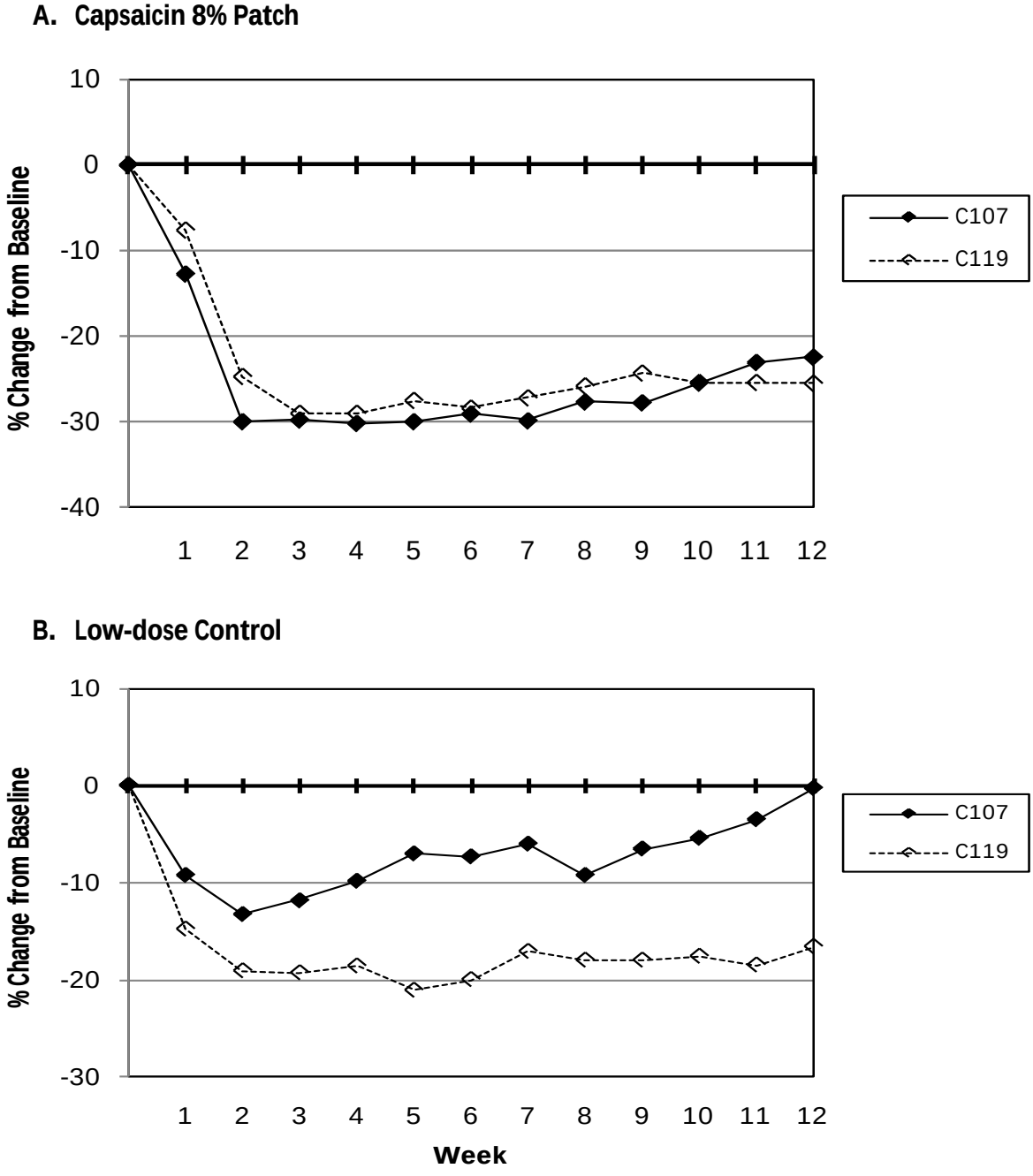


NPRS = Numeric Pain Rating Scale.

In comparing Study C107 to C119, the weekly mean percent change from Baseline during Weeks 2 to 12 in the 30-minute Capsaicin 8% Patch groups was generally similar. Both studies also demonstrated the same temporal pattern and magnitude of response: for Study C107 (range: -22% to -30%) and Study C119 (range: -24% to -29%) (Figure 12).

In both studies, the Capsaicin 8% Patch subjects in the total groups and in the 30-minute groups had greater pain reductions than the Control groups beginning at Week 2 and continuing at each subsequent week through Week 12. In Study C107, the Control group responses were smaller than those observed in Study C119 and tended to return to Baseline NPRS scores toward the end of the study (Figure 12). In Study C119, the Control response appeared to be "stable" from Week 2 to Week 12 because the NPRS scores in the 60 minute low-dose Control group improved during this time period. By contrast, the 30-minute low-dose Control arm in Study C119 behaved as it did all 3 control arms in Study C107 (i.e., trending to return to Baseline NPRS scores over time).

Figure 12 **Weekly LS Mean Percent Change in NPRS Score from Baseline in the 30-minute Capsaicin 8% Patch Group, Studies C107 and C119**

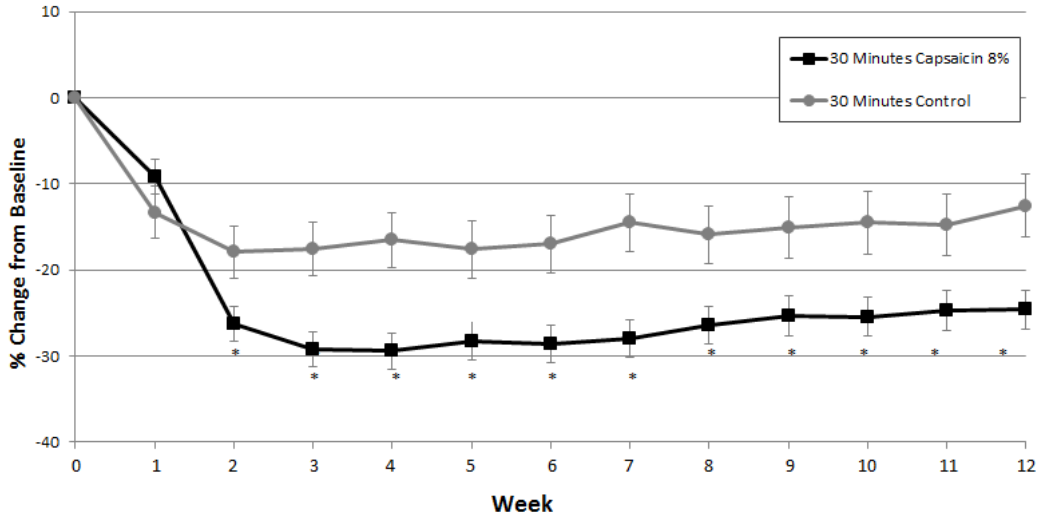


LS = least squares; NPRS=Numeric Pain Rating Scale.

A summary of the mean percent change in "average pain for the past 24 hours" NPRS scores from Baseline is presented by week for the 30-minute application duration for the integrated dataset in Figure 13.

Comparison of the LS mean percent change from Baseline in NPRS scores by week for the integrated dataset demonstrated that a 30-minute treatment with the Capsaicin 8% Patch was associated with a slightly higher average pain level during Week 1 compared to the 30-minute low- dose Control group. After week 1, 30-minute treatment with the Capsaicin 8% Patch continued to be associated with decreasing NPRS scores from Baseline compared to the 30-minute low-dose Control group and was significantly greater than Control beginning at Week 2. Significant reductions in NPRS scores were maintained at each subsequent week through Week 12. At Week 12, the 30-minute Capsaicin 8% Patch group had a mean percent change from Baseline in NPRS score of -25% (P = 0.0051) compared with -13% for the 30-minute low-dose Control group. The 60-minute Capsaicin 8% Patch group had only small, non-significant differences from the Control group.

Figure 13 **Weekly LS Mean Percent Change in "Average Pain for the Past 24 Hours" NPRS Score from Baseline, Integrated Dataset**

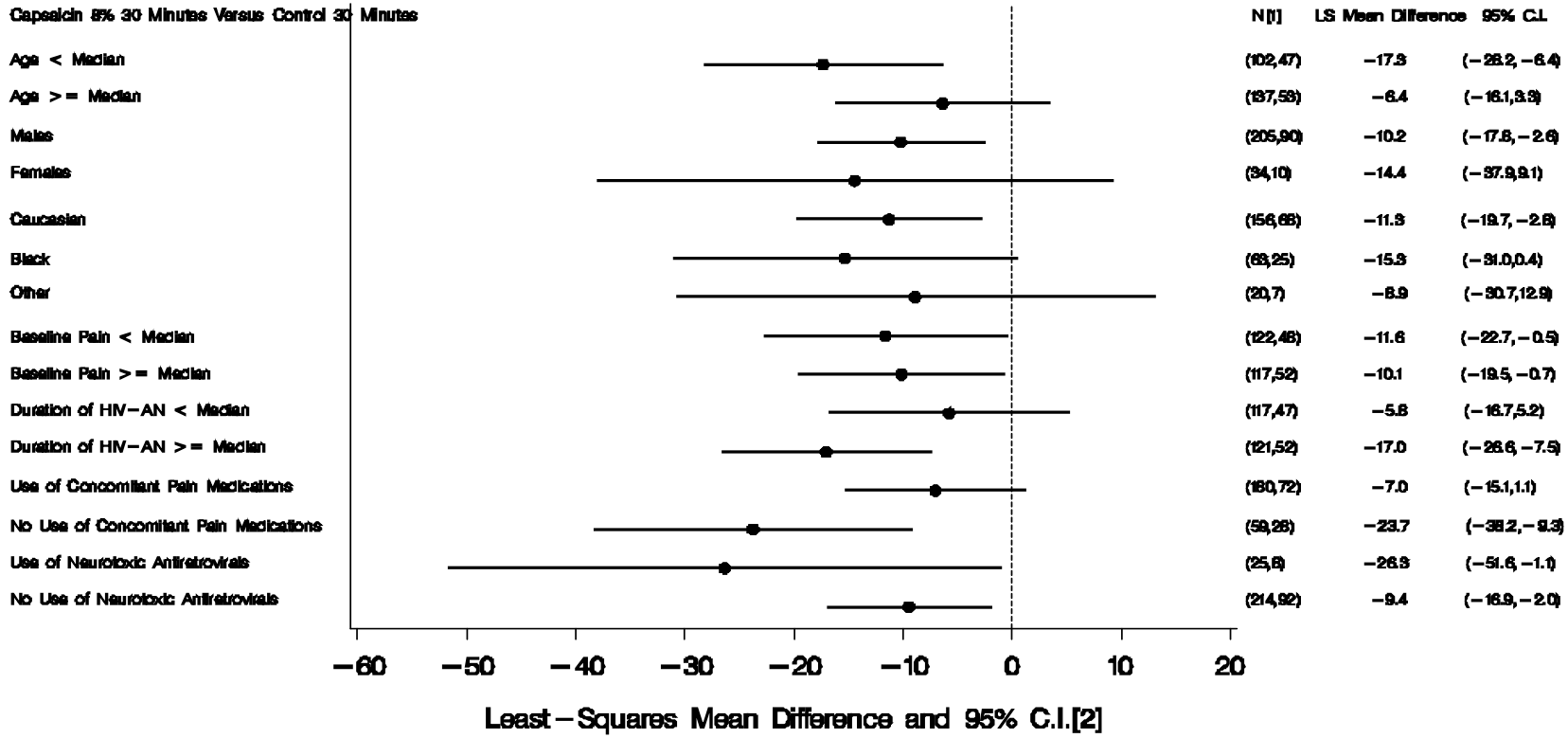


LS = least squares; NPRS = Numeric Pain Rating Scale.
*P < 0.05

Capsaicin 8% Patch treatment for 30 minutes consistently resulted in greater improvements in NPRS scores, as assessed by mean percent change in pain scores during Weeks 2 to 12, and responder rate (≥30% decrease in NPRS score from Baseline) compared with 30-minute low-dose Control treatments, in all subgroups regardless of gender, age, race, Baseline pain score, concomitant neuropathic pain medication use, HIV-PN duration, and neurotoxic antiretroviral use (Figure 14). Treatment differences and odds ratios favored the 30-minute Capsaicin 8% Patch treatment regardless of gender, age, race, Baseline pain score, duration of HIV-PN, use of neurotoxic antiretroviral, and use of concomitant neuropathic pain medication. Treatment differences between the 30-minute Capsaicin 8% Patch group and the 30-minute low-dose Control group were larger in subjects not using concomitant neuropathic pain medications compared with those using concomitant neuropathic pain medications. Similar findings were observed in Capsaicin 8% Patch PHN studies.

As shown in Figure 14, Capsaicin 8% Patch 30-minute treatment subjects who were not taking concomitant pain medications had a greater pain reduction from Baseline in Weeks 2 to 12 compared to 30-minute low-dose Control treatment subjects who were using concomitant pain medications (-24% versus -7.0%), with overlapping 95% CI. This is a potentially important finding since it suggests that the Capsaicin 8% Patch provides analgesic benefit for both the treatment-naïve, as well as treated, HIV-PN subjects who continue to have pain. Given that over two-thirds of subjects enrolled in the Capsaicin 8% Patch HIV-PN studies were taking concomitant neuropathic pain medications, the observed magnitude of pain reduction in the treatment-naïve versus treated subject populations suggests that greater analgesic efficacy of the Capsaicin 8% Patch might be observed by excluding subjects using concomitant analgesics and/or requiring that all other neuropathic pain medications be withdrawn prior to study entry.

Figure 14 **Studies C107 and C119: Percent Change in "Average Pain for the Past 24 Hours" NPRS Scores from Baseline to Weeks 2-12 LOCF by Subgroup Least-Squares Mean Difference/95% Confidence Intervals**



ANCOVA = analysis of covariance, CI = confidence interval, HIV-PN = human immunodeficiency virus-associated peripheral neuropathy, LS = Least Squares, NPRS = Numeric Pain Rating Scale.

Note: LS Mean Differences and 95% CIs were computed using a gender-stratified (except for the subgroup of gender) ANCOVA model to test for difference between Capsaicin 8% Patch 30-minute low-dose Control 30-minute groups, with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as covariates.

[1]N = (n of 30-minute Capsaicin 8% Patch group, n of 30-minute low-dose Control group).

6.4 Assessment of Efficacy Limiting Factors

Although the data presented above provide a substantial amount of evidence to support the efficacy, it is of relevance that at least 2 important factors can be identified that appear to have limited the observed efficacy signal:

1. As a shown above in Figure 13, the use of concomitant analgesic medications was associated with a smaller efficacy signal. By design in both Studies C107 and C119, concomitant analgesic medications were allowed to be used by up to 75% of subjects. The rationale for allowing concomitant analgesic medications was based on an ethical concern: allowing only analgesic free subjects into the trials would have required that many subjects would have had to withdraw from their existing analgesic medications. However, based on the analysis above, a larger efficacy signal would have likely resulted had subjects been required to discontinue concomitant analgesic use during the trials.

2. Study C119 differed from Study C107 in that it included clinical trials sites outside the United States (i.e., in the United Kingdom, Canada and Australia) (Table 20). In retrospect and unexpectedly, the extension of the study to these non-US sites led to an increase in the variability of response. For example, the low-dose Control subjects in the 60-minute application group in Canadian sites had an increase in NPRS pain scores of 1.2% from Baseline to Weeks 2 to 12 whereas, in Australia and all US sites, subjects within this group reported a 46% and a 31% NPRS pain score reduction from Baseline, respectively. This introduces variability in the primary endpoint data. To address this variability rank transformations of the primary endpoint responses were used for the non-parametric ANCOVA analysis. As a result, in retrospect, non-parametric statistical tests to assess the primary endpoint would have been a potential analysis method. Indeed, as shown in Table 15, the results of the rank analysis of covariance in Study C119, adjusting for gender and with Baseline pain, pre-LMX4 pain, and percent change in pain during LMX4 application as a covariate, showed a significant ($P = 0.0147$) difference between the total Capsaicin 8% Patch and Control groups and also between the 30-minute Capsaicin 8% Patch and the 30-minute control group ($P = 0.0251$).

Table 20 **Summary of Percent Change in "Average Pain for the Past 24 Hours" NPRS Scores from Baseline during Weeks 2 to 12 by Country**

Percent Change in NPRS Score from Baseline during Weeks 2 to 12	Control			Capsaicin 8% Patch		
	30 min	60 min	Total	30 min	60 min	Total
	N = 73	N = 89	N = 162	N = 167	N = 165	N = 332
All Sites, n	73	89	162	167	165	332
LS Mean (SE)	- 19.1 (3.61)	- 30.1 (3.27)	- 24.6 (2.43)	- 26.1 (2.39)	- 32.8 (2.41)	- 29.5 (1.70)
All US Sites, n	55	66	121	125	130	255
LS Mean (SE)	- 16.2 (4.22)	- 30.8 (3.85)	- 23.5 (2.86)	- 25.5 (2.80)	- 32.1 (2.75)	- 28.8 (1.97)
All Canadian Sites, n	1	3	4	5	2	7
LS Mean (SE)	- 67.5 (43.28)	1.2 (22.17)	- 33.2 (26.86)	- 28.2 (15.62)	- 23.4 (24.32)	- 25.8 (14.50)
All UK Sites, n	8	11	19	21	15	36
LS Mean (SE)	- 21.7 (8.27)	- 19.8 (7.07)	- 20.8 (5.47)	- 19.6 (5.14)	- 32.2 (6.01)	- 25.9 (3.95)
All Australian Sites, n	9	9	18	16	18	34
LS Mean (SE)	- 27.8 (10.65)	- 45.8 (10.75)	- 36.8 (7.50)	- 39.1 (8.47)	- 37.0 (7.51)	- 38.1 (5.74)

LS Mean: Least Squares Mean; NPRS: Numeric Pain Rating Scale; SE: Standard Error; UK: United Kingdom; US: United States

Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day - 14 through Day - 1, inclusive. Missing scores on or prior to Day 8 were estimated using the Baseline score; missing scores after Day 8 were estimated using the previous non-missing score. If all post-treatment NPRS scores were missing, then Baseline score was used for imputation.

6.5 Efficacy Conclusions from the Integrated Analysis

The exploratory integrated analyses provide strong and consistent evidence that a 30-minute application of the Capsaicin 8% Patch is significantly superior to a low-dose Control patch (P = 0.0024), resulting in a treatment difference of -11% in daily NPRS scores (95% CI: -18.3, -4.0). These results are robust and generally independent of the analyses methods used (i.e., parametric or nonparametric statistical tests).

Secondary endpoint results of the integrated analyses also support the finding that a 30-minute application of the Capsaicin 8% Patch is nominally statistically significantly superior to a 30-minute low-dose Control treatment (e.g., proportion of responders: 40% versus 23%, respectively; P = 0.0040). Subjects treated with Capsaicin 8% Patch for 30 minutes had 2.2-fold higher odds of responding compared with the 30-minute low-dose Control group. The Kolmogorov-Smirnov test demonstrated a significant difference in the distribution of cumulative responses rate over time between the total and the 30-minute Capsaicin 8% Patch

groups versus the Control groups (P = 0.0097 and 0.0053, respectively). These results all confirm the robustness of the efficacy results for the 30-minute Capsaicin 8% Patch application time group.

Larger pain reductions in those treated with the Capsaicin 8% Patch compared with those treated with Control were observed as early as the second week following treatment compared with those treated with Control. This difference between Capsaicin 8% Patch and Control was maintained at each subsequent week through Week 12.

Nominally statistically significant improvements as measured by PGIC were consistently observed among subjects treated with Capsaicin 8% Patch for 30 minutes in the integrated dataset. The PGIC data demonstrate that HIV-PN subjects reported a global clinical benefit of treatment following a 30-minute treatment with the Capsaicin 8% Patch at 12 weeks post-treatment. This result provides corroborative evidence that the observed reduction in daily pain intensity as measured by the NPRS scores was clinically meaningful to the HIV-PN subjects.

7. Integrated Analysis of Safety in the HIV-PN Development Program

The overall safety database for treatment with Capsaicin 8% Patch consists of data from all 15 clinical trials: 2 trials with healthy volunteers and 13 trials in subjects with peripheral neuropathic pain (HIV, PHN, and PDN).

A total of 2464 subjects were enrolled in these 15 studies. Of these 2464 subjects, 1696 subjects (685 with HIV-PN, 920 with PHN and 91 with PDN) have received at least one treatment with a Capsaicin 8% Patch, including 634 unique HIV-PN subjects.

The integrated safety analysis for HIV-PN will be limited to the 806 subjects (560 Capsaicin 8% Patch and 246 low-dose Control) who were evaluated in the controlled HIV-PN studies (i.e., studies C107, C112 and C119). A total of 560 subjects received a Capsaicin 8% Patch treatment (N=239, 246 and 75, respectively, for 30-, 60- and 90-minute application of Capsaicin 8% Patch) in the context of a double-blind controlled trial.

Overall, the surveillance adopted to capture AEs was generally consistent across all studies. AEs were monitored and tracked from the time of local anesthetic application through study termination. AEs that were ongoing were followed until AE resolution or 30 days after the last treatment. Vital signs were measured at each visit and physical exams were conducted at baseline and Week 12 (or termination). Laboratory assessments were performed at Baseline and Week 12 (or termination) in the controlled studies. At screening, during treatment, and final visits, a targeted neuropathy exam was performed in all studies.

In the first 4 studies that included HIV-PN subjects (i.e., C107, C109, C111, and C112), application site pain, erythema and burning that occurred on the day of treatment were tracked by NPRS and dermal assessment scores and, by protocol instruction, were therefore not recorded as AEs. By contrast, in Study C119, application site pain, erythema and burning that occurred on the day of treatment were reported as AEs, as were dermal assessment score changes of $\geq$2 units.

7.1 Extent of Repeat Dose Exposure

A total of 337 subjects received treatment in open-label studies that allowed for repeated applications of the Capsaicin 8% Patch (i.e., Study C107 open-label extension phase and Study C118). Of these 337 subjects, 137, 76, 75, and 49 received 1, 2, 3, and 4 treatments, respectively. Of these 337 subjects who had repeated applications of Capsaicin 8% Patch, 272

were originally enrolled in the double-blind portion of Study C107 who elected to receive, and met the criteria for, retreatment. These subjects received the 60-minute treatment only. The remaining 65 subjects were treated in Studies C109, C111, and C118 and were randomized to receive 60- or 90-minute applications.

7.2 Most Common Treatment-Emergent Adverse Events in Controlled HIV-PN Studies

The overall incidence of treatment-emergent AEs in the total Capsaicin 8% Patch group (86%) was higher compared with the total low-dose Control group (73%) (Table 21). The difference was due primarily to the expected higher incidence of application site AEs. There was no apparent relationship with patch application duration. Additional analyses did not suggest any relationship with treatment area.

Table 21 **Number (%) of Subjects with the Most Common Treatment Emergent Adverse Events (≥3% of Subjects in Either Total Treatment Group) by Treatment Duration (Controlled Studies of HIV-PN Subjects)**

System Organ Class Preferred Term, n (%)	Low-dose Control				Capsaicin 8% Patch			
	30 min N = 99	60 min N = 118	90 min N = 29	Total N = 246	30 min N = 239	60 min N = 246	90 min N = 75	Total N = 560
Number of Subjects Reporting ≥1 Treatment-Emergent Adverse Events	77 (78)	89 (75)	14 (48)	180 (73)	205 (86)	222 (90)	53 (71)	480 (86)
Gastrointestinal Disorders	13 (13)	8 (6.8)	2 (6.9)	23 (9.3)	31 (13)	25 (10)	11 (15)	67 (12)
Diarrhea	3 (3.0)	1 (0.8)	2 (6.9)	6 (2.4)	7 (2.9)	8 (3.3)	6 (8.0)	21 (3.8)
General Disorders and Administration Site Conditions	52 (53)	63 (53)	8 (28)	123 (50)	181 (76)	204 (83)	39 (52)	424 (76)
Application Site Dryness	1 (1.0)	1 (0.8)	2 (6.9)	4 (1.6)	9 (3.8)	15 (6.1)	9 (12)	33 (5.9)
Application Site Erythema	24 (24)	34 (29)	0	58 (24)	80 (34)	97 (39)	0	177 (32)
Application Site Pain	36 (36)	31 (26)	4 (14)	71 (29)	153 (64)	161 (65)	25 (33)	339 (61)
Application Site Papules	0	1 (0.8)	0	1 (0.4)	10 (4.2)	11 (4.5)	2 (2.7)	23 (4.1)
Application Site Pruritus	1 (1.0)	3 (2.5)	3 (10)	7 (2.8)	18 (7.5)	20 (8.1)	13 (17)	51 (9.1)
Application Site Swelling	2 (2.0)	2 (1.7)	3 (10)	7 (2.8)	4 (1.7)	13 (5.3)	14 (19)	31 (5.5)
Fatigue	2 (2.0)	2 (1.7)	0	4 (1.6)	9 (3.8)	8 (3.3)	1 (1.3)	18 (3.2)
Infections and Infestations	19 (19)	20 (17)	6 (21)	45 (18)	53 (22)	69 (28)	21 (28)	143 (26)
Upper Respiratory Tract Infection	7 (7.1)	3 (2.5)	0	10 (4.1)	14 (5.9)	14 (5.7)	9 (12)	37 (6.6)
Musculoskeletal and Connective Tissue Disorders	10 (10)	15 (13)	5 (17)	30 (12)	37 (16)	30 (12)	15 (20)	82 (15)
Pain in Extremity	2 (2)	4 (3)	2 (7)	8 (3)	10 (4)	11 (5)	0	21 (4)
Arthralgia	1 (1)	0	1 (3)	2 (0.8)	6 (3)	6 (2)	6 (8)	18 (3)
Nervous System Disorders	17 (17)	14 (12)	6 (21)	37 (15)	32 (13)	29 (12)	10 (13)	71 (13)
Peripheral Sensory Neuropathy	12 (12)	7 (5.9)	0	19 (7.7)	7 (2.9)	5 (2.0)	0	12 (2.1)

System Organ Class Preferred Term, n (%)	Low-dose Control				Capsaicin 8% Patch			
	30 min	60 min	90 min	Total	30 min	60 min	90 min	Total
Headache	2 (2.0)	2 (1.7)	1 (3.4)	5 (2.0)	6 (2.5)	7 (2.8)	4 (5.3)	17 (3.0)
Skin and Subcutaneous Tissue Disorders	3 (10)	13 (11)	14 (14)	30 (12)	7 (9.3)	21 (8.5)	21 (8.8)	49 (8.8)
Erythema	0	5 (4.2)	4 (4.0)	9 (3.7)	1 (1.3)	2 (0.8)	3 (1.3)	6 (1.1)

NOTES:

1. At each level of summation (overall, system organ class, preferred term), subjects reporting more than one AE are counted only once.
2. Adverse events with onset date on or after the first day of treatment are included.
3. Data for Capsaicin 8% Patch 90 minutes and low-dose Control 90 minutes were derived from Study C107 (double-blind portion only).
4. Data for Capsaicin 8% Patch 60 minutes and low-dose Control 60 minutes were derived from Studies C107 (double-blind portion only), C112, and C119.
5. Data for Capsaicin 8% Patch 30 minutes and low-dose Control 30 minutes were derived from Study C107 (double-blind portion only) and C119.
6. Data for total Capsaicin 8% Patch and total low-dose Control includes all doses from all studies.

Table 22 shows the most common treatment-emergent AEs that the investigators judged as severe. Most of the severe events occurring with Capsaicin 8% Patch were application site pain.

Table 22 Number (%) of Subjects with the Most Common Severe Adverse Events (n≥2 Subjects in Either Total Treatment Groups) by Treatment Duration (Controlled Studies in HIV-PN Subjects)

Preferred Term, n (%)	Low-dose Control				Capsaicin 8% Patch			
	30 min N = 99	60 min N = 118	90 min N = 29	Total N = 246	30 min N = 239	60 min N = 246	90 min N = 75	Total N = 560
Number of Subjects Reporting ≥1 Treatment-Emergent Severe Adverse Events	10 (10)	8 (7)	5 (17)	23 (9)	37 (16)	62 (25)	18 (24)	117 (21)
Application Site Pain	3 (3)	0	0	3 (1)	25 (11)	43 (18)	6 (8)	74 (13)
Peripheral Sensory Neuropathy	3 (3)	1 (0.8)	0	4 (2)	0	0	0	0

NOTES:

1. At each level of summation (overall, system organ class, preferred term), subjects reporting more than one adverse event is counted only once using the highest severity.
2. Adverse events with an onset date on or after the first day of treatment are included. Adverse events that occurred during the open-label extensions, but prior to the next treatment were counted according to the treatment received in the double-blind, controlled phase.
3. Data for Capsaicin 8% Patch 90 minutes and low-dose Control 90 minutes were derived from Study C107 (double-blind portion).
4. Data for Capsaicin 8% Patch 60 minutes and low-dose Control 60 minutes were derived from Studies C107 (double-blind portion), C112, and C119.
5. Data for Capsaicin 8% Patch 30 minutes and low-dose Control 30 minutes were derived from Studies C107 (double-blind portion) and C119.
6. Pooled data includes all doses from HIV-PN controlled studies.

7.2.1 Most Common Treatment-Emergent Adverse Events in Repeat Application HIV-PN Studies

In general, the pattern of AEs was similar to that observed in the single-application, controlled studies, with application site reactions accounting for the majority of AEs. Within the individual AE of application site erythema, there was a gradual increased incidence with the number of exposures (first [9.5%], second [13%], third [18%], and fourth [20%]). However, other application site AEs (e.g. papules, pruritus, and vesicle) generally decreased in incidence

over time or did not change. Since Study C107 did not record dermal AEs associated with the patch (using the dermal scoring scale instead), the dermal assessment scores obtained during this study are a more appropriate measure of local site reactions , as opposed to the incidence of application site AEs. In a separate analysis of Study C118 (not shown), there was no increase in application site erythema and pain with repeated administration.

7.3 Serious Adverse Events in Controlled HIV-PN Studies

The overall incidence of serious adverse events (SAEs) reported for HIV-PN subjects participating in a controlled study was 6% in both the total Capsaicin 8% Patch group and the low-dose Control group (Table 23), and all SAEs were considered to be of remote or no relationship to study medication. Table 23 shows the SAEs in the controlled HIV-PN studies for events reported in two more subjects in either combined dose group.

Table 23 **Number (%) of Subjects with the Most Common Treatment-Emergent Serious Adverse Events (≥2 Subjects in Any Combined Group) (Controlled Studies of HIV-PN Subjects)**

Preferred Term, n (%)	Low-dose Control				Capsaicin 8% Patch			
	30 min N = 99	60 min N = 118	90 min N = 29	Total N = 246	30 min N = 239	60 min N = 246	90 min N = 75	Total N = 560
Treatment-Emergent Serious Adverse Events Reported in ≥2 Subjects	3 (3)	8 (7)	4 (14)	15 (6)	10 (4)	19 (8)	5 (7)	34 (6)
Appendicitis	0	0	0	0	0	1 (0.4)	1 (1)	2 (0.4)
Cholecystitis	0	0	0	0	0	2 (0.8)	0	2 (0.4)
Lower Respiratory Tract Infection	0	0	0	0	0	2 (0.8)	0	2 (0.4)
Myocardial Infarction	0	2 (2)	0	2 (0.8)	0	0	0	0
Pneumonia	0	0	0	0	1 (0.4)	1 (0.4)	0	2 (0.4)

NOTES:

1. At each level of summation (overall, preferred term), subjects reporting more than one serious adverse event are counted only once.
2. Serious adverse events with an onset date on or after the first day of treatment are included. Adverse events that occurred during the open-label extensions, but prior to the next treatment were counted according to the treatment received in the double-blind, controlled phase.
3. Data for Capsaicin 8% Patch 90 minutes and low-dose Control 90 minutes were derived from Study C107 (double-blind portion).
4. Data for Capsaicin 8% Patch 60 minutes and low-dose Control 60 minutes were derived from Studies C107 (double-blind portion), C112, and C119.
5. Data for Capsaicin 8% Patch 30 minutes and low-dose Control 30 minutes were derived from Studies C107 (double-blind portion) and C119.
6. Pooled data includes all doses from HIV-PN controlled studies.

In the repeat-dose experience, there were 28 SAEs and no obvious relationship with the duration of use. Taken together, the incidence of SAEs did not increase with the number of treated subjects over time. The number of subjects with at least one reported SAE was: 16 (4.7%) with 1 treatment, 7 (3.5%) for 2 treatments, 3 (2.4%) for 3 treatments, and 2 (4.2%) for 4 treatments. No single SAE was experienced by more than 1 subject.

All SAEs reported across the repeat-treatment studies of HIV-PN subjects were considered to be of remote or no relationship to study medication, with one exception. Subject 1206, a 59-year-old Black male with a medical history of HIV disease and distal symmetrical polyneuropathy (DSP), was hospitalized overnight for pain in his treatment area.

On Day 0 (04 May 2004), the subject received an initial double-blind Capsaicin 8% Patch treatment for 60 minutes without incident. He was re-treated at his Week 12 Visit on Day 90 (2 August 2004) with open-label Capsaicin 8% Patch for 60 minutes. The subject experienced some burning sensation and itching in the treated area during and after removal of the patches, which was managed with oxycodone, cool gauze, and cold water. The subject was able to complete the full 60-minute application. The pain level after treatment was within an expected range and no further actions were required to manage the pain. At the scheduled time for discharge from the clinic (2 hours post patch removal) the subject expressed anxiety about managing his pain alone. He was admitted overnight for observation and convenience of assistance for the subject. The burning pain in the treatment area and itchy feet were considered resolved at 4 hours post-patch removal. The subject was discharged on Day 91 with no burning sensation or itching from the treatment and no neuropathic pain. The investigator reported the event as probably related to study medication.

7.4 Adverse Events Leading to Discontinuation in the HIV-PN Studies

Of the 685 HIV-PN subjects treated with NGX-4010 in All HIV-PN Studies, 14 (2%) withdrew from the study due to an AE; 4 of these AEs (all application site pain) were considered related to study drug. The remaining 10 AEs (rectal cancer recurrent, hepatic enzyme increased, pregnancy, pain exacerbated, increase in HIV viral load, arthritis, cellulitis staphylococcal, hepatitis C, cholecystitis, and right should injury post fall) were assessed as remote or not related to study drug.

7.5 Clinical Laboratory Findings

In both controlled trials C107 and C119, hematology and chemistry values were determined at Screening and Week 12/Termination. Shifts in individual hematology and chemistry parameters from normal to abnormal are summarized in Table 24.

Although the great majority of laboratory values were similar across treatment groups, there were two exceptions noted. These consisted of:

1) A higher proportion of subjects had a decrease in platelet counts (3.4% versus 1.0%)
2) A higher proportion of subjects had an increase in AST (8.1% versus 2.8%).

Table 24 Shifts in Clinical Laboratory Values from Normal at Screening to Abnormal at Week 12/Termination (Controlled Studies in HIV-PN Subjects)

Clinical Laboratory Parameter, n (%)	Low-dose Control (N = 246)		Capsaicin 8% Patch (N = 560)	
	Normal to Low	Normal to High	Normal to Low	Normal to High
Hematology				
Hematocrit	15 (7)	1 (0.5)	32 (7)	3 (0.6)
White Blood Cells (WBC)	13 (6)	3 (1)	34 (7)	7 (2)
Platelet Count	2 (1)	2 (1)	16 (3)	2 (0.4)
CD4, Absolute	5 (8)	0	15 (9)	1 (0.6)
Chemistry				
Blood Urea Nitrogen (BUN)	1 (0.5)	5 (2)	5 (1)	20 (4)
Creatinine	5 (2)	3 (1)	2 (0.4)	5 (1)
Chloride	8 (4)	1 (0.5)	7 (1)	9 (2)
Potassium	3 (1)	0	10 (2)	1 (0.2)
Sodium	8 (4)	1 (0.5)	14 (3)	1 (0.2)

Clinical Laboratory Parameter, n (%)	Low-dose Control (N = 246)		Capsaicin 8% Patch (N = 560)	
	Normal to Low	Normal to High	Normal to Low	Normal to High
Alkaline Phosphatase	1 (0.5)	7 (3)	1 (0.2)	18 (4)
AST	0	6 (3)	0	39 (8)
ALT	0	12 (6)	0	28 (6)

ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; DB=double-blind; Low=below the normal reference range; High=above the normal reference range; WBC=white blood cell count.

NOTES:

1. Data derived from Studies C107 (DB portion), C112, and C119.
2. Summary includes only subjects with values at both Screening and Week 12/Termination. Change was calculated as value at Week 12/Termination minus value at Screening. If there was more than one Screening assessment, the earliest was used.

Platelet Decrease Observation:

There was a noted decrease in patients classified as low platelets (n=16; 3.4%) in the Capsaicin 8% Patch subject population relative to the control group (n=2; 1.0%). Given that the Capsaicin 8% Patch is topically delivered and has almost no detectable systemic absorption, it is unlikely that treatment for a maximum of 90 minutes could cause these changes observed 12 weeks after application.

In contrast, thrombocytopenia is not uncommon in HIV infected patients and can occur for reasons ranging from the HIV virus itself, to a variety of medications used to treat HIV. In evaluation of these subjects, 5 were thought to have clinically significant decreases and were also noted to have significant co-morbid conditions including pneumonia, diabetes mellitus with unstable glucose, multiple HIV medications, and an increase in HIV viral loads during the study, as well as several individuals with baseline low normal platelet and WBC levels.

Additional co-infection with other viruses such as HCV or HBV can also be a causal factor. However, there was only a slight increase in co-infection in the Capsaicin 8% Patch treatment group versus Control, when all data were pooled (C107 = Pooled Capsaicin 8% Patch = 51/225 or 22.7% and Control = 15/82 or 18.3%; C119 Pooled Capsaicin 8% Patch = 77/332 or 23.2% and Control = 35/162 or 21.6%; both C107 + C119 Pooled Capsaicin 8% Patch = 128/557 or 23% and Control = 50/244 or 20.5%). Based on this observation, it is unlikely that the small difference in co-infection was a significant causal factor.

There was also a modest increase in the proportion of patients using “Neurotoxic Retrovirals” at baseline for the Capsaicin 8% Patch (11%) relative to the Control (8.4%) groups. In addition, there was almost a 2x increase in viral RNA load in the pooled Capsaicin 8% Patch

subjects versus the pooled Control subjects ($41.8x10^3$ RNA/mL versus $19.3x10^3$ RNA/mL, respectively). In summary, while not definitive, the differences across treatment groups in the use of some HIV medications as well as HIV status and the complicated co-morbid conditions and concurrent illnesses sustained by a number of the subjects discussed above, could explain the observed decrease in platelets observed in the trial.

AST Elevation Observation:

There was a greater proportion of patients (8.1%) classified as "Normal to High" for Aspartate Aminotransferase (AST) relative to the pooled control (2.8%). AST is a non-specific enzyme found in liver as well as brain, skeletal muscle, kidneys, and lung. Examination of the Capsaicin 8% Patch pooled data shows that 34 of the 39 patients listed had AST elevations of less than 2x the upper limit of normal (ULN) with 21 patients in the 30 minute application group, 12 in the 60 minute application group, and 1 in the 90 minute application group. Four additional patients in the active groups had AST elevations of 2x and 3x in the 60 minute group and 1 patient in the 30 minute application group had an elevation of 5x ULN.

The exact etiology of the observed difference across treatment groups is unknown. Possibilities include drug induced liver toxicity from concomitant medications, other liver disease (e.g., cirrhosis, etc.), elevation of LFTs due to HIV itself, co-infections (e.g., HCV), and lastly, due to chance. Drug induced liver toxicity would not be unusual in this population. There are suggestions in the medical literature that HIV can be associated with elevated liver function tests and some medications used for HIV may be associated with liver abnormalities, specifically protease inhibitors. As discussed above, there a slight imbalance in the use of "Neurotoxic Antiretrovirals at Baseline" with 28/557 (11%) pooled Capsaicin 8% Patch subjects using these medications versus 18/215 (8.4%) of control patients. Although small in magnitude, this difference could be one of several comorbid causal factors. Examination of the pooled demographics for other medications does not show an obvious imbalance in the use of analgesics (i.e., opioids, antidepressants, and anticonvulsants) across the Capsaicin 8% Patch and the Control group, so these concomitant analgesics are an unlikely cause. It is unclear from the demographics whether there was a difference in use of EtOH or APAP, which could affect AST as well as other markers. Lastly, given that Capsaicin 8% Patch is topical with almost no detectable blood levels after application, and that these LFT abnormalities were noted 12 weeks after application, it seems quite unlikely that the noted abnormalities are due to the Capsaicin 8% Patch.

Other liver conditions such as chronic cirrhosis are possible causes but are unlikely without concurrent elevations of other more specific liver function test markers (e.g., ALT and Alkaline

Phosphatase). Co-elevations of these markers could suggest other underlying liver problems (e.g., cirrhosis, bile duct stenosis, etc.). Note that bilirubin was not collected in this study. In addition, as discussed above, there was a markedly greater RNA load in the pooled Capsaicin 8% Patch group ($41.8x10^3$ RNA/mL) versus Control ($19.3x10^3$ RNA/mL) or a 2+ increase in the active group. While not definitive, this difference may also explain some of the difference in AST levels. As discussed above in the section on platelets, co-infection with Hepatitis B & C viruses may have had a small contribution.

In conclusion, although no one clear etiology stands out to explain the observed difference, examination of shift tables and demographics does suggests two main factors may explain the pattern observed: an increased HIV RNA viral load in the active Capsaicin 8% Patch group versus the low-dose Control group and a modest increase in neurotoxic retrovirals use in the Capsaicin 8% Patch group at Baseline.

7.6 Vital Signs

In both controlled trials C107 and C119, vital signs were measured at all study visits. Table 25 provides a summary of the mean change in vital signs over time Overall there was no obvious clinically meaningful trend in blood pressure (BP), heart rate, or respiratory rate changes when viewed over the duration of the studies. However, there were both BP and HR changes observed in both the control and active groups during the patch application period. The only observation of note was that small increases in heart rate were seen in both the Capsaicin 8% Patch and low-dose Control groups, with a greater magnitude change (approximately 1-2 beats per minute [bpm]) in the Capsaicin 8% Patch group, at Weeks 4, 8 and 12. The clinical significance of these changes is unclear. The incidence of AEs that might suggest sympathetic nervous system dysfunction (e.g., hypotension or syncope) was low in these trials and comparable in frequency across the Capsaicin 8% Patch and low-dose Control groups. In addition, an analysis of the pooled data across all controlled and open-label HIV-PN studies did not reveal an obvious trend of clinically meaningful heart rate increase with repeated applications. In summary, the observed small increase in heart rate in the Capsaicin 8% Patch versus low-dose Control groups is not considered clinically significant.

Table 25 Mean Change in Vital Signs over Time (Controlled Studies in HIV-PN Subjects)

	Low-dose Control		Capsaicin 8% Patch	
Change from Screening	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Systolic BP (mmHg)				
Screening	245	123 (15)	559	124 (14)
Change at Week 4	226	0.2 (15)	527	-0.8 (15)
Change at Week 8	153	-0.3 (15)	308	0.3 (15)
Change at Week 12	179	0.4 (14)	416	-0.5 (15)
Diastolic BP (mmHg)				
Screening	245	77.7 (11)	559	77.8 (10)
Change at Week 4	226	-0.7 (10)	527	-0.6 (10)
Change at Week 8	153	-0.7 (11)	308	0.1 (11)
Change at Week 12	179	-0.1 (11)	416	-0.6 (10)
Heart Rate (bpm)				
Screening	245	74.3 (11)	558	74.4 (12)
Change at Week 4	226	1.0 (12)	528	2.3 (11)
Change at Week 8	153	1.2 (12)	308	3.5 (12)
Change at Week 12	179	0.4 (12)	416	2.9 (11)
Respiratory Rate (breaths/min)				
Screening	245	16.2 (2.7)	555	16.3 (2.7)
Change at Week 4	225	0.2 (2.7)	523	0.0 (2.4)
Change at Week 8	153	0.1 (2.6)	302	0.3 (2.6)
Change at Week 12	177	0.1 (2.8)	411	0.4 (2.6)

BP = blood pressure, bpm = beats per minute, DB = double-blind, mmHg = millimeters of mercury, SD = standard deviation.
NOTE: Pooled data (30, 60, and 90 minutes) were derived from Studies C107 (DB portion), C112, and C119.

7.7 Deaths

Throughout the HIV-PN clinical development program, a total of 7 subjects died: 6 in Study C107 and 1 in Study C119. These deaths were all deemed to be of remote or no relationship to Study Drugs by the investigators. A listing of the observed deaths and study drug exposure is provided in Table 26.

In most cases, death occurred more than 60 days after dosing (i.e., study day number). In addition, the listed causes of death appear consistent with the co-morbid conditions that typically accompany HIV. Although 5 of the 7 deaths occurred in the Capsaicin 8% Patch treatment group, a causal relationship to Capsaicin 8% Patch treatment is unlikely based on the medical histories, comorbid conditions, and the topical capsaicin mechanism of action.

Table 26 Cause of Death and Study Exposure Time – Study 107 and Study 119

Study No.	Subject (Sex/Age)	Treatment Group	Cause of Death	Study Day Number
C107	M/51	60-min Capsaicin 8% Patch	Sepsis	7
C107	M/47	90-min low-dose Control	Unknown (Collapsed at home; coma)	89
C107	M/45	60-min low-dose Control	Presumed Drug Overdose	22
C107	F/37	60-min Capsaicin 8% Patch	Pneumonia	138
C107	M/42	60-min Capsaicin 8% Patch (open label portion)	Pneumonia	114
C107	M/40	30-min Capsaicin 8% Patch	Suicide	108
C119	M/54	60-min Capsaicin 8% Patch	Arteriosclerotic Cardiovascular Disease	68

7.8 Special Safety Topics- Response to Treatment

Vital signs, NPRS scores and Dermal Scores were assessed on the day of treatment. Results from these assessments, integrated from controlled studies C107 and C119, are discussed below.

7.8.1 "Pain Now" NPRS Scores (Treatment Application Visit)

Mean (+/-SE) changes in "pain now" NPRS scores prior to, during, and after patch application are depicted in Figure 15. During patch application, mean NPRS scores are comparable across Capsaicin 8% Patch treatment groups. After patch removal, the NPRS scores in the 30-minute treatment arm during the immediate post patch removal period are lower than those in the other groups. Table 27 summarizes the NPRS "pain now" score during and after the patch application. Consistent with Figure 15, the 30-minute Capsaicin 8% Patch treatment provides the lowest average maximum change in NPRS "pain now" score during and after patch application compared the longer treatment duration arms. As shown in Table 27, 42% of subjects in the 30-minute Capsaicin 8% Patch arm experienced an increase in NPRS score of >2 points on the treatment day compared to 57% and 47% for 60- and 90-minute arms, respectively.

All Capsaicin 8% Patch treatment groups had a higher maximum change in NPRS scores than low-dose Control patch group and this difference reached statistical significance in all analyses

during and after the Capsaicin 8% Patch application. However, it should be noted that the average maximal pain scores after application of the Capsaicin 8% Patch were only approximately 0.5 above the Baseline pain score on the 0 to 10 NPRS.

Figure 15 **Mean (+/-SE) Changes in NPRS Scores Prior to during and after Patch Application**

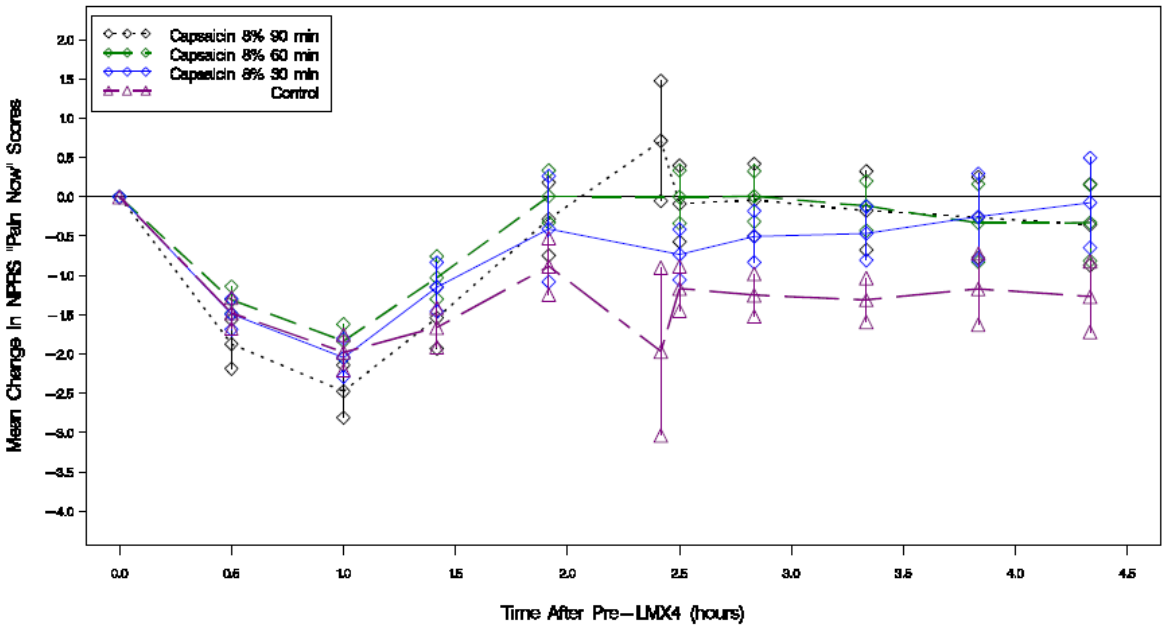


Table 27 Summary of Tolerability on the Treatment Day by Treatment Duration (Controlled Studies in HIV-PN Subjects)

	Low-dose Control	Capsaicin 8% Patch			
Change from Baseline[a]	**Total**	**30 min**	**60 min**	**90 min**	**Total**
Maximum Change in NPRS Score during LMX4^{O} Application					
N	246	239	246	75	560
Mean (SD)	-1.0 (2)	-1.0 (2)	-0.8 (2)	-1.1 (2)	-1.0 (2)
Maximum Change in NPRS Score during and after Patch Application[b]					
N	246	239	246	75	560
Mean (SD)	0.4 (2)	2.1 (3)	2.8 (3)	2.7 (3)	2.5 (3)
Change in NPRS Score on the day of the Last Observation [b]					
N	246	239	246	75	560
Mean (SD)	-0.1 (2)	1.5 (3)	2.2 (3)	1.8 (3)	1.8 (3)
Number (%) of Subjects with an Increase in NPRS Score on Day 0 of > 2 Points					
Yes	32 (13)	100 (42)	140 (57)	35 (47)	275 (49)
No	214 (87)	139 (58)	106 (43)	40 (53)	285 (51)

DB=double blind; LMX4®=topical anesthetic; NPRS=Numeric Pain Rating Scale; SD=standard deviation.

NOTE: Studies included for treatment duration are: 30 minutes=C107 (DB portion) and C119; 60 minutes=C107 (DB portion), C112, and C119; 90 minutes=C107 (DB portion).

[a]Change from preLMX4^{O} time point.

[b]Includes the evening of the treatment day.

7.8.2 Dermal Assessment Score (Treatment Visit)

At the Treatment Visit, dermal assessments were made prior to application of the topical anesthetic, immediately after removal of the topical anesthetic, immediately after patch removal and at 2 hours after Capsaicin 8% Patch removal.

Dermal assessment was based upon the following rating scale.

0 = no evidence of irritation;
1 = minimal erythema, barely perceptible;
2 = definite erythema, readily visible/minimal edema or minimal papular response;
3 = erythema and papules;
4 = definite edema;

5 = erythema, edema, and papules;
6 = vesicular eruption;
7 = strong reaction spreading beyond test site.

For double-blind studies, the number and percent of subjects in each dermal assessment category were presented at each time point. For treatment group comparisons, the dermal assessment scores were condensed into the categories 0, 1, or ³ 2. Each Capsaicin 8% Patch active treatment group was compared with the pooled Control group using the Mantel-Haenszel exact test. The 2-sided p-value was used.

For the change in dermal assessment scores from the pre-topical anesthetic (preLMX4^{Ò}) application, the number of subjects with ³ 2 units change in dermal assessment scores were compared across treatment groups (each Capsaicin 8% Patch active treatment group versus the pooled Control group) using a Cochran-Mantel-Haenszel test of general association.

Table 28 provides a summary of maximum dermal assessments scores during the Treatment Visit as well as a summary of the proportion of subjects who experienced a dermal assessment score increase of >2 points, A greater proportion of subjects in the Capsaicin 8% Patch group had experienced a dermal assessment score increase of >2 points (28% versus 8.1%) and this increase was dose dependent. In addition, there was a dose dependent shift toward higher maximum dermal score. While the maximum scores in the 30-minute treatment group were significantly higher than those in the low-dose Control group, no subject in this treatment group experienced a score greater than 3.

Table 28 **Maximum Dermal Assessment Scores and Number (%) of Subjects with a Maximum Increase ³ 2 Points on the Day of Treatment (Controlled Studies in HIV-PN Subjects)**

	Low-dose Control	Capsaicin 8% Patch			
	Total (N = 246)	30 min (N = 239)	60 min (N = 246)	90 min (N = 75)	Total (N = 560)
Maximum Score on Day 0, n (%)					
0 = No evidence of irritation	143 (58)	111 (46)	88 (36)	21 (28)	220 (39)
1 = Minimal erythema, barely perceptible	75 (31)	66 (28)	69 (28)	25 (33)	160 (29)
2 = Definite erythema, readily visible, minimal edema or papular response	27 (11)	58 (24)	77 (31)	25 (33)	160 (29)
3 = Erythema and papules	1 (0.4)	4 (2)	8 (3)	3 (4)	15 (3)
4 = Definite edema	0	0	2 (0.8)	0	2 (0.4)
5 = Erythema, edema, and papules	0	0	1 (0.4)	1 (1)	2 (0.4)
6 = Vesicular eruption	0	0	0	0	0
7 = Strong reaction spreading beyond test site	0	0	1 (0.4)	0	1 (0.2)
Maximum Increase ≥ 2 Points, n (%)					
Yes	20 (8.1)	51 (21)	80 (33)	28 (37)	159 (28)
No	226 (92)	188 (79)	166 (68)	47 (63)	401 (72)

DB=double blind.

NOTES:

1. NGX-4010 90-minute data were derived from Study C107 (DB portion).
2. NGX-4010 60-minute data were derived from Studies C107 (DB portion), C112, and C119.
3. NGX-4010 30-minute data were derived from Study C107 (DB portion) and C119.
4. Pooled Control data (30, 60, and 90 minutes) were derived from Studies C107 (DB portion), C112, and C119.

7.8.3 Blood Pressure Changes (Treatment Visit)

The maximum changes in vital signs on the day of treatment by treatment duration are summarized in Table 29. An application time dependent increase in maximum change in SBP, DBP, HR and RR was seen in the pooled Capsaicin 8% Patch group that was numerically greater in all cases than those seen in the low-dose Control group. However, in almost all cases the magnitude of the Capsaicin 8% Patch increase was less than 1x that of the control group.

Overall, there was a modest application time response effect with the largest numerical BP increases observed for the 90 min >60 min > 30 min groups.

Changes in SBP (mean +/- SE) on the day of treatment in Studies C107 and C119 are depicted graphically in Figure 16 and Figure 17, respectively. In each graph, with study time shown in minutes, both a patch application time dependent response can be seen. At the last timepoint measurement (i.e., 115 minutes post application of the patch), the mean levels of systolic blood pressure in the 30 minute Capsaicin 7% Patch application time group overlapped with those in the low-dose Control group in each study. In summary, the BP changes were observed to be coincident with the application site reactions, particularly pain, and trended to return to Baseline values after patch removal, particularly in the 30 minute dose group.

Table 29 Maximum Change in Vital Signs on the Day of Treatment by Treatment Duration (Controlled Studies in HIV-PN Subjects)

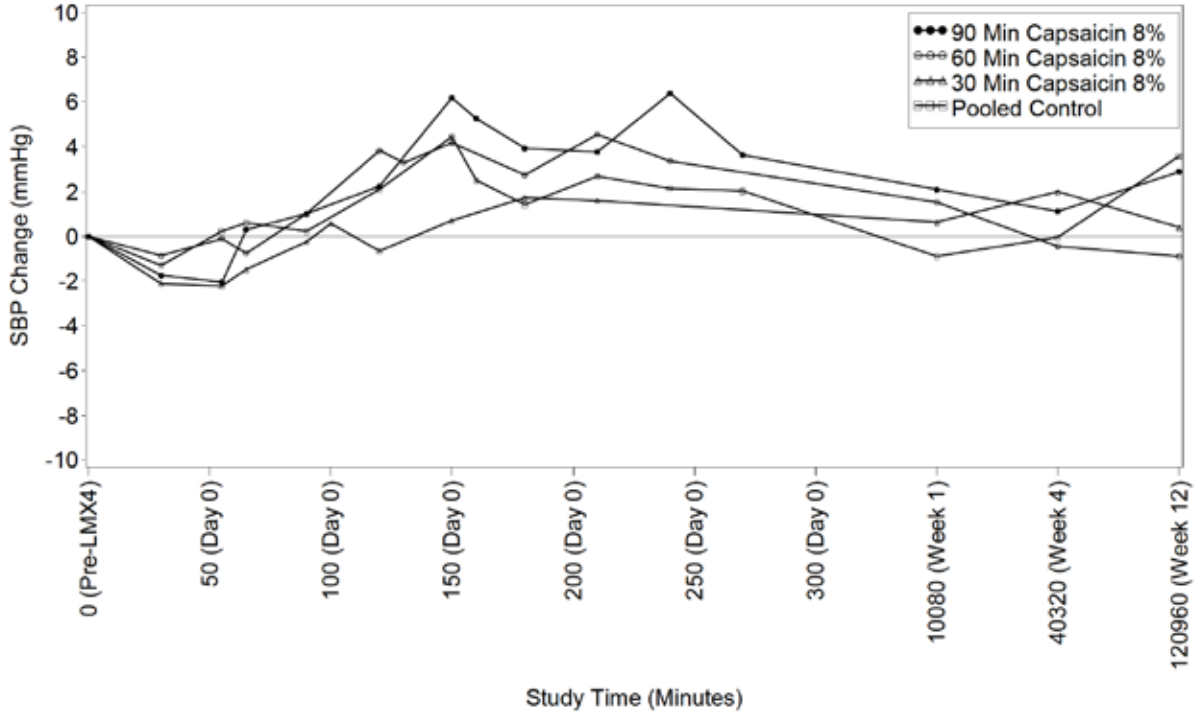
	Low-dose Control		Capsaicin 8% Patch	
	N	Mean (SD)	N	Mean (SD)
Systolic BP (mmHg)				
Total	246	8.1 (11)	560	11.1 (13)
90 minutes	29	12 (109)	75	15.9 (14)
60 minutes	118	8.7 (11)	246	10.9 (14)
30 minutes	99	6.2 (11)	239	9.7 (11)
Diastolic BP (mmHg)				
Total	246	6.6 (8)	560	7.6 (8)
90 minutes	29	9.2 (7)	75	9.7 (8)
60 minutes	118	6.3 (8)	246	7.9 (8)
30 minutes	99	6.2 (8)	239	6.7 (8)
Heart Rate (bpm)				
Total	246	3.5 (7)	560	4.9 (8)
90 minutes	29	5.3 (7)	75	7.9 (9)
60 minutes	118	3.1 (7)	246	4.9 (7)
30 minutes	99	3.5 (7)	239	3.9 (8)
Respiratory Rate (breaths/min)				
Total	246	1.1 (2)	559	1.5 (3)
90 minutes	29	1.6 (2)	74	2.3 (3)
60 minutes	118	1.2 (2)	246	1.6 (3)
30 minutes	99	0.8 (2)	239	1.3 (2)

BP=blood pressure; bpm=beats per minute; DB=double blind; LMX4®=topical anesthetic; mmHg=millimeters of mercury; SD=standard deviation.

NOTES:

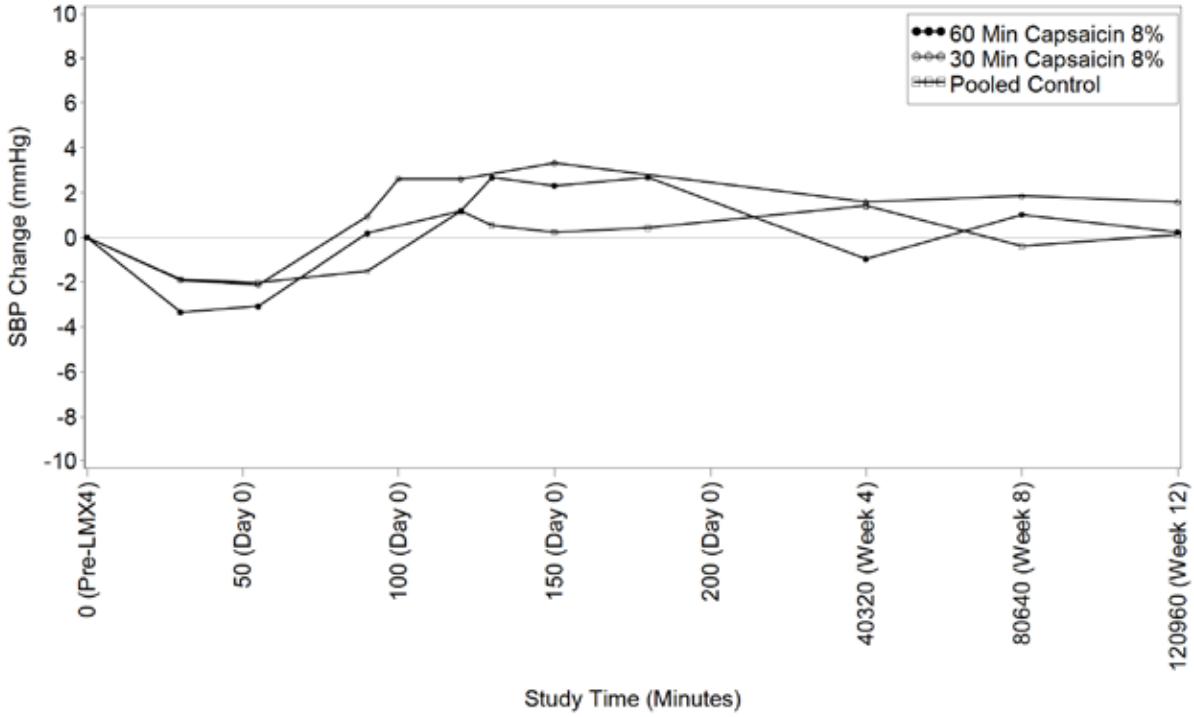
1. Treatment duration data (30, 60, and 90 minutes) were derived from Studies C107 (DB portion), C112, and C119.
2. Maximum change during and after patch application from preLMX4 time point.

Figure 16 **Changes in Systolic Blood Pressure (Mean ± SE) during 12- Week Study Period—Study C107**



SBP=systolic blood pressure; Active = Capsaicin 640 mcg/cm^2, Control = Capsaicin 3.2 mcg/cm^2

Figure 17 **Changes in Systolic Blood Pressure (Mean ± SE) during 12-Week Study Period —Study C119**



SBP=systolic blood pressure; Active = Capsaicin 640 mcg/cm^2, Control = Capsaicin 3.2 mcg/cm^2

7.8.4 Targeted Neuropathy Examination Rating Scale

There was no evidence of impairment of neurological sensory function in HIV-PN subjects overall or by treatment duration (30, 60, and 90 minutes) following treatment with the Capsaicin 8% Patch. Overall, an assessment of changes between Screening and Week 12/Termination in 194 HIV-PN subjects and 74 Control subjects (n=193 and n=73, respectively, for warmth) showed no differences between the Capsaicin 8% Patch treated subjects and Control. The majority (70% to 91%) of subjects in both treatment groups had "no change" for deep tendon reflex, or for vibration, warmth, or sharp sensation. Of those subjects with changes, in both groups more subjects demonstrated "increased" (i.e., improved compared to baseline values), vibration, warmth, and sharp sensations whereas a slightly higher proportion of subjects demonstrated "decreased" deep tendon reflexes.

7.9 Overall Summary of Safety

More than 90% of enrolled subjects in the controlled trials of HIV-PN (i.e., Studies C107 and C119) completed the study and less than 1% terminated prematurely due to an adverse event or death. The adverse event profile in both controlled studies was similar. As expected, application site related adverse events predominated and, in general, were treatment duration dependent. Such reactions were typically short-lived (1 to 7 days in duration) but did require an increased use of analgesic medication in the Capsaicin 8% Patch treated subjects during Week 1.

Overall there does not appear to be an obvious relationship between systemic side effects and treatment with Capsaicin 8% Patch. This lack of systemic side effects is consistent with the low systemic exposure of capsaicin (i.e., less than 0.5 ng/ml in subjects treated for 60 minutes or less) and its metabolites. Transient increases in BP and HR were seen in association with study drug application and with the exception of a small 2 to 3 bpm increase observed at 12 weeks in the pooled Capsaicin 8% Patch-treated subjects, did not persist over time.

Finally, there is no evidence of clinically meaningful neurological dysfunction induced in subjects based on a subgroup analysis in individuals who underwent targeted clinical neuropathy assessments and quantitative sensory testing over time.

7.9.1 Post-Marketing Experience

The Capsaicin 8% Patch has been commercially available in the U.S. and the European Union and was first launched in Germany on 15 March 2010. The global safety of Capsaicin 8% Patch is reviewed on an ongoing basis by NeurogesX. Adverse event reports are received from all sources including clinical studies, spontaneous reports, regulatory authorities, published literature, and from post marketing surveillance studies. The data provided here include all AEs reported from March 2010 to 15 November 2011. These data have been analyzed in a cumulative setting to identify any potential new safety signals. No actions have been taken for safety reasons by either a regulatory authority or by any Marketing Authorization Holder (MAH) concerning withdrawal, rejection, suspension, or failure to obtain a renewal of a Marketing Authorization. There have been no restrictions on distribution, clinical study suspension, dosage modification, changes in target population, indications, or formulation changes. In summary, there have been no label changes based on the post-marketing experience.

7.9.2 Exposure

The cumulative marketing subject exposure (as of 15 November 2011) is estimated to be approximately 8866 subjects. The post-approval cumulative clinical trial exposure from March 2010 to 15 November 2011 is 263 subjects. Therefore cumulative subject exposure as of 15 November 2011, including the cumulative clinical exposure (n=263) and cumulative marketing exposure (n=8866) is estimated to be about 9129 subjects.

7.9.3 Post-Marketing Adverse Events

For the post-marketing safety summary, the NeurogesX clinical safety database was searched from the date of launch (March 2010) to 15 November 2011, to identify all post-marketing reports (i.e., both spontaneous and post-marketing surveillance). Based on these data, no new safety signal has been identified. This review confirms the known safety profile of Capsaicin 8% Patch and that the current and proposed product labeling accurately reflects this profile.

A total of 1370 AEs including 232 SAEs were reported. The most frequently reported AEs occurring at a frequency greater than 1.0% were application site pain (507 total AEs, 40 of which were serious) for a crude incidence rate of 5.6% (i.e., 507/9129 patients) and application site erythema (293 total AEs, 9 of which were serious) resulting in a crude incidence rate of 3.2%. The following postmarketing SAEs listed by preferred term that occurred 2 or more times and that did not appear in the U.S. prescribing information (PI) included: bradycardia, cardiovascular disorder, abdominal pain upper, vomiting, ascites, application site pain, application site vesicles, asthenia, pain, product quality issue, death, influenza, pneumonia, dizziness, presyncope, somnolence, hyperhidrosis, and hypotension. Four deaths occurred during the post-marketing period but these were reported as unrelated to study medication.

Although AEs and SAEs are considered to be related to study drug when spontaneously reported, the Sponsor considers most of the unlabeled AEs and SAEs reported unrelated to Capsaicin 8% Patch treatment but related to pre-existing morbidity, co-administered medication, or other causes. Those unlisted but considered related, such as application site reactions, are of very low incidence and are not considered of sufficient clinical significance warrant a change in the product's risk benefit profile at this time.

For the post-marketing safety summary, the NeurogesX clinical safety database was searched from the date of launch (March 2010) to 15 November 2011, in order to identify all post-marketing reports (i.e., both spontaneous and post-marketing surveillance). Based on these data no new safety signal has been identified. This review confirms the known safety profile of

Capsaicin 8% Patch and that the current and proposed product labeling accurately reflects this profile.

8. RISK/BENEFIT DISCUSSION

The totality of the data from the Capsaicin 8% Patch (640 µg capsaicin/cm^2; 8% w/w) clinical development program supports the conclusion that treatment with a Capsaicin 8% Patch for 30 minutes is both safe and effective for the management of neuropathic pain associated with HIV-PN. In addition, an assessment of the risk/benefit of this product provides a compelling rationale for approval based on 3 main considerations:

1. Pain associated with HIV-PN is a major unmet medical need for which no therapies have been approved

HIV-PN is a peripheral neuropathic pain condition that is the most common neurological complication of HIV infection and a major cause of morbidity [Verma 2001; Ellis 2010]. A recent study found that over half of HIV subjects evaluated had signs of HIV sensory neuropathy and nearly 40% of these subjects reported neuropathic pain [Ellis 2010]. Patients with HIV-PN predominantly report symptoms in their feet, including pain, paresthesias and numbness. Despite the widespread use of effective combination anti-retroviral therapy (not thought to be neurotoxic), the prevalence of HIV-PN continues to be high. Unfortunately, medicines used to reduce pain in other neuropathic pain syndromes have yielded disappointing results in randomized, controlled studies in subjects with HIV-PN. To date, no medicines have been approved by the FDA for the management of neuropathic pain associated with HIV-PN. The availability of a topical, localized therapeutic option would constitute an important advance in the management of pain in subjects with HIV-PN. In addition, the topical administration of the Capsaicin 8% Patch, applied no more than once every 12 weeks, would not add to the 'pill burden', which is substantial in the HIV population due to the treatment regimens used to control HIV and its comorbidities.

2. The Capsaicin 8% Patch has demonstrated substantial evidence of clinically meaningful pain reduction in subjects with pain associated with HIV-PN

The totality of the data from Studies C107 and C119 provides substantial evidence of clinical efficacy for the Capsaicin 8% Patch in the treatment of painful neuropathy associated with HIV-PN. Although a formal regulatory definition of "substantial evidence" does not exist, the term is usually defined as a body of relevant evidence that is adequate to support a conclusion. In this case, the prespecified primary endpoint analysis from Study C107, the prespecified secondary endpoint analyses from Studies C107 and C119, and the analyses of the integrated dataset provide an adequate amount of evidence that leads to a reasonable conclusion

supporting the clinical efficacy of the Capsaicin 8% Patch in the treatment of painful neuropathy associated with HIV-PN.

The data from pivotal Study C107 provide robust statistical evidence that treatment with the Capsaicin 8% Patch provides a clinically meaningful reduction of pain for up to 12 weeks after a single application in HIV-PN compared with the low-dose Control (-23% versus -11%, P = 0.0026 using the prespecified analysis method). This effect was observed regardless of gender, age, race, Baseline pain score, concomitant neuropathic pain medication use, HIV-PN duration, and neurotoxic antiretroviral use. These results were confirmed in the 90-minute application time cohort (using the prespecified analysis method) and were similar in the 30-minute application time cohort compared to the total Control cohort, based on exploratory statistical analyses.

The results of Study C119, despite being unable to meet the prespecified statistical efficacy endpoint at a $P < 0.05$ level, support the findings of Study C107. Subjects treated with the Capsaicin 8% Patch had a greater reduction in mean percent change in NPRS scores from Baseline to Weeks 2 to 12 compared with the low-dose Control group (-30% versus -25%, P = 0.0967 using the prespecified analysis methods). The 30-minute application time group reported a 26% decrease in pain compared with a 19% decrease in the low-dose Control group (P = 0.1031).

Analyses of multiple prespecified secondary endpoints, summarized below, also support the conclusion from the primary endpoint analysis that Capsaicin 8% Patch treatment for 30 minutes is effective in the management of neuropathic pain associated with HIV-PN:

- In both Phase 3 studies, treatment with Capsaicin 8% Patch for 30 minutes resulted in a higher responder rate (≥ 30% reduction in pain from Baseline during Weeks 2 to 12) compared with low-dose Control. In Study C107, using the prespecified analysis method, 42% of those treated with Capsaicin 8% Patch for 30 minutes were responders compared with 18% of those treated with low-dose Control (P = 0.0017). In study C119, using the prespecified analysis method, 39% of those treated with Capsaicin 8% Patch for 30 minutes were responders compared with 26% of those treated with low-dose Control (P = 0.0553). These results were confirmed by the results of integrated analysis of the responder rates from C107 and C119 studies demonstrated that Capsaicin 8% Patch applied for 30 minutes is superior to the low-concentration capsaicin control treatment (proportion of responders: 40% versus 23%, respectively; P = 0.0040); subjects treated with the Capsaicin 8% Patch for 30 minutes had 2.2-fold higher odds of responding compared with the 30-minute Control group.

- Treatment with the Capsaicin 8% Patch for 30 minutes in Studies C107 and C119 resulted in a distribution of PGIC responses at Week 12/Termination that was significantly different from low-dose Control and in a higher proportion of subjects who rated themselves as being improved compared with low-dose Control. When pooled across the two studies, 65% of subjects treated with Capsaicin 8% Patch for 30 minutes felt improved at Week 12/Termination compared with 41% of low-dose Control subjects.

- In Study C107, statistically significant improvements were observed for the recommended 30-minute Capsaicin 8% Patch dose across the Gracely Pain Scale, the BPI, and the SFMPQ.

- In Study C119, statistically significant improvements were observed for the recommended 30-minute Capsaicin 8% Patch dose for mean SF 36v2 scores (including several subcategories) and the SAT questionnaire.

Pain reductions were larger for 30-minute Capsaicin 8% Patch groups compared with low-dose Control groups beginning by Week 2 after administration, and these differences were maintained for the remainder of the 12-week double-blind study phase.

The duration of efficacy, as measured by the time to first retreatment during the 40-week, open-label extension portion of Study C107, was statistically significantly longer for the total Capsaicin 8% Patch group compared with the total low-dose Control group (median time to retreatment 18 versus 13 weeks; P = 0.0022). Similar findings were observed in the PHN population receiving repeated treatments [Backonja 2010].

In addition, two key factors were identified that appear to have negatively impacted the efficacy signal. First, the results indicate that the observed efficacy signal may have been diluted by allowing up to 75% of the subjects in both studies to use concomitant analgesic medications. Second, given the greater variability observed in the C119 trial conducted across multiple geographic locations, use of nonparametric statistical tests would have been an alternative analysis approach to testing efficacy rather than the prespecified parametric tests used in the study.

3. The Capsaicin 8% Patch is safe and well tolerated.

Less than 1% of the HIV-PN subjects terminated the studies due to a treatment-related AE. The most common AEs accounting for these withdrawals were transient application site pain, erythema, and pruritus, which are similar to the application site reactions experienced by treated PHN patients. The Capsaicin 8% Patch was not associated with cumulative toxicity following multiple treatment cycles. Safety data collected during the clinical development program support the conclusion that Capsaicin 8% Patch is generally safe and well tolerated.

The incidence of AEs associated with BP changes in both the total Capsaicin 8% Patch and total low-dose Control groups was low (<3%). The incidence of increased BP was slightly higher in Capsaicin 8% Patch subjects (1.1%) compared with low-dose Control subjects (0.4%), reflecting the small, transient increases in BP that were seen on the day of treatment, coincident with treatment-related changes in pain scores. The Capsaicin 8% Patch did not appear to be associated with any other systemic AEs, a finding not unexpected given the uncommon, transient, low level of systemic capsaicin exposure observed after topical application of Capsaicin 8% Patch.

As expected, greater increases in mean NPRS scores were reported in subjects treated with Capsaicin 8% Patch compared with low-dose Control subjects during and shortly after patch application. Mean NPRS scores returned to Baseline by the end of Day 2 and subsequently remained, on average, at or below Baseline levels over the remainder of the 12-week studies.

Sequential neurological testing during the clinical development program indicated that, in HIV-PN subjects, Capsaicin 8% Patch treatment is not associated with any clinically evident detrimental effect on sensory function. In serial tests performed in subjects who received more than one treatment with Capsaicin 8% Patch, no adverse neurological effects of repeated application were observed, providing evidence that exposure to Capsaicin 8% Patch administered up to 4 times over 1 year does not impair protective sensory function in subjects with neuropathic pain.

The Capsaicin 8% Patch is associated with few central nervous system adverse effects or other serious systemic adverse effects, unlike the systemic medications that are used for the treatment of neuropathic pain. The Capsaicin 8% Patch treatment is not complicated by drug-drug interactions since the systemic exposure to capsaicin is minimal. A low risk for systemic adverse events and drug-drug interactions is therefore a major benefit for HIV patients who already use extensive drug regiments to control the infection and its effects.

In summary, based on the safety profile of Capsaicin 8% Patch, the risk involved with this treatment is assessed to be very low compared with systemic neuropathic pain treatments that would typically be used in this patient population.

Conclusion

There is substantial evidence that treatment with Capsaicin 8% Patch provides a clinically meaningful reduction of pain for up to 12 weeks after a single 30-minute application in subjects with neuropathic pain associated with HIV-PN. The treatment is very well tolerated and is not associated with important systemic, neurological or sensory-related adverse effects. Treatment-related AEs are primarily transient and include mild to moderate application site reactions. Transient, very small elevations in BP (averaging <3 mm Hg) occur during patch application and are coincident with treatment-related discomfort and pain.

Therefore, the Capsaicin 8% Patch provides clinical benefits that far outweigh its risks for the many patients suffering from pain associated with HIV-PN.

9. REFERENCE LIST

Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo controlled trial. Neurology. 2007;68(7):515-521.

Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br J Anaesth. 2011;107(4):490-502.

Babbar S, Marier JF, Mouksassi MS, et al. Pharmacokinetic analysis of capsaicin after topical administration of a high-concentration capsaicin patch to patients with peripheral neuropathic pain. Ther Drug Monit. 2009;31(4):502-510.

Backonja MM, Malan TP, Vanhove GF, Tobias JK; C102/106 Study Group. NGX-4010, a high concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double blind, controlled study with an open label extension. Pain Med. 2010;11(4):600-608.

Bhangoo SK, Ripsch MS, Buchanan DJ, Miller RJ, White FA. Increased chemokine signaling in a model of HIV1-associated peripheral neuropathy. Mol Pain. 2009;5:48.

Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron. 2006;52(1):77-92.

Chaiyasit K, Khovidhunkit W, Wittayalertpanya S. Pharmacokinetics and the effect of capsaicin in Capsicum frutescens on decreasing plasma glucose level. J Med Assoc Thai. 2009;92(1):108-113.

Chanda S, Bashir M, Babbar S, Koganti A, Bley K. *In vitro* hepatic and skin metabolism of capsaicin. Drug Metab Dispos. 2008;36(4):670-675.

Committee of Experts on Flavouring Substances. Active Principles: Datasheet on Capsaicin. October 2005, pp. 59-67.

Cordell GA, Araujo OE. Capsaicin: identification, nomenclature, and pharmacotherapy. Ann Pharmacother. 1993;27(3):330-336.

Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain. 1983;17(2):197-210.

Dworkin RH, Turk DC, Farrar JT, et al; IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19.

Dworkin, RH, Turk DC, Katz NP, et al. Evidence based clinical trial design for the chronic pain pharmacotherapy: A blue print for ACTION. Pain. 2011;152(3Suppl):S107-115.

Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 2009;34(3):672-680.

Ellis RJ, Rosario D, Clifford DB, et al. Continued high prevalence and adverse clinical impact of human immunodeficiency virus associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER Study. Arch Neurol. 2010;67(5):552-558.

Estanislao L, Olney R, McArthur J, and the Lidoderm HIV neuropathy study group. A randomized placebo controlled trial of 5% lidocaine gel for HIV-associated distal symmetric polyneuropathy. J AIDS. 2004;37(5):1584-1586.

Evans SR, Ellis RJ, Chen H, et al. Peripheral neuropathy in HIV: prevalence and risk factors. AIDS. 2011;25(7):919-928.

Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11 point numerical pain rating scale. Pain. 2001;94(2):149-158.

Govindarajan VS, Sathyanarayana MN. Capsicum production, technology, chemistry, and quality. Part V. Impact on physiology, pharmacology, nutrition, and metabolism; structure, pungency, pain, and desensitization sequences. Crit Rev Food Sci Nutr. 1991;29(6):435-474.

Gracely RH, McGrath F, Dubner R. Ratio scales of sensory and affective verbal pain descriptors. Pain. 1978;5(1):5-18.

Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. Pain. 2011;152(1):14-27.

Hahn K, Arendt G, Braun JS, et al. A placebo controlled trial of gabapentin for painful HIV associated sensory neuropathies. J Neurol. 2004;251(10):1260-1266.

Harden N, Cohen M. Unmet needs in the management of neuropathic pain. J Pain Symptom Manage. 2003;25(5 Suppl):S12-S17.

Hochberg. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75(4):800-802.

Holzer P. The pharmacological challenge to tame the transient receptor potential vanilloid-1 (TRPV1) nocisensor. Br J Pharmacol. 2008;155(8):1145-1162.

Jensen TS, Baron R, Haanpää M, et al. A new definition of neuropathic pain. Pain. 2011;152(10):2204-2205.

Kemper CA, Kent G, Burton S, et al. Mexiletine for HIV infected patients with painful peripheral neuropathy: a double blind, placebo controlled, crossover treatment trial. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;19(4):367-372.

Kennedy WR, Vanhove GF, Lu SP, et al. A randomized, controlled, open-label study of the long-term effects of NGX-4010, a high-concentration capsaicin patch, on epidermal nerve fiber density and sensory function in healthy volunteers. J Pain. 2010;11(6):579-587.

Kieburtz K, Simpson D, Yiannoutsos C, et al. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. Neurology.1998;51(6):1682-1688.

Koch GG, Amara IA, Davis GW, Gillings DB. A review of some statistical methods for covariance analysis of categorical data. Biometrics. 1982;38(3):553-595.

Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical data analysis. In Berry DA, ed., Statistical Methodology in Pharmaceutical Sciences. New York: Marcel Dekker, 1990;291-475.

Malmberg AB, Mizisin AP, Calcutt NA, von Stein T, Robbins WR, Bley KR. Reduced heat sensitivity and epidermal nerve fiber immunostaining following single applications of a high-concentration capsaicin patch. Pain. 2004;111(3):360-367.

Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. Biometrika. 1976;63(3):655-660.

McArthur JC, Yiannoutsos C, Simpson DM, et al. A phase II trial of nerve growth factor for sensory neuropathy associated with HIV infection. Neurology. 2000;54:1080-1088.

Melzack R. The short form McGill Pain Questionnaire. Pain. 1987;30(2):191-197.

National Research Council: The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data on Clinical trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC; National Academies Press; 2010.

Paice JA, Ferrans CE, Lashley FR, Shott S, Vizgirda V, Pitrak D. Topical capsaicin in the management of HIV-associated peripheral neuropathy. J Pain Symptom Manage. 2000;19(1):45-52.

Pershing LK, Reilly CA, Corlett JL, Crouch DJ. Effects of vehicle on the uptake and elimination kinetics of capsaicinoids in human skin *in vivo*. Toxicol Appl Pharmacol. 2004;200(1):73-81.

Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS. Pharmacological treatment of painful HIV associated sensory neuropathy: a systematic review and meta analysis of randomised controlled trials. PLoS One. 2010;5(12):e14433.

Quade D. Rank analysis of covariance. J Amer Stat Assoc.1967;62:1187-1200.

Reilly CA, Yost GS. Structural and enzymatic parameters that determine alkyl dehydrogenation/hydroxylation of capsaicinoids by cytochrome P450 enzymes. Drug Metab Disopos. 2005;33(4):530-536.

Schifitto G, Yiannoutsos C, Simpson DM, et al. Long-term treatment with recombinant nerve growth factor for HIV associated sensory neuropathy. Neurology. 2001;57(7);1313-1316.

Schifitto G, Yiannoutsos CT, Simpson DM, et al. A placebo controlled study of memantine for the treatment of human immunodeficiency virus associated sensory neuropathy. J Neurovirol. 2006;12(4):328-31.

Shapiro, SS, Wilk MB. An analysis of variance test for normality (complete samples). Biometrika. 1965;52(34):591-611.

Shlay JC, Chaloner K, Max MG, et al. Acupuncture and amitriptyline for pain due to HIV related peripheral neuropathy: a randomized clinical trial. JAMA. 1998;280(18):1590-1595.

Simpson DM, Dorfman D, Olney RK, et al. Peptide T in the treatment of painful distal neuropathy associated with AIDS: results of placebo controlled trial. Neurology 1996;47(5):1254-1259.

Simpson DM, McArthur JC, Olney R, et al. Lamotrigine for HIV associated painful sensory neuropathies: a placebo controlled trial. Neurology. 2003;60(9):1508-1514.

Simpson DM, Schifitto G, Clifford DB, et al. Pregabalin for painful HIV neuropathy: a randomized, double blind, placebo controlled trial. Neurology. 2010;74(5):413-420.

Stokes, ME, Davis CS, Koch G. Categorical Data Analysis using the SAS System, Cary, NC: SAS Institute Inc. 1995;499.

Szallasi A, Blumberg PM. Vanilloid (capsaicin) receptors and mechanisms. Pharmacol Rev. 1999;51(2):159-212.

Szolcsanyi J. Forty years in capsaicin research for sensory pharmacology and physiology. Neuropeptides. 2004;38:377-384.

Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: Redefinition and grading system for clinical research purposes. Neurology. 2008;70(18):1630-1635.

US Food and Drug Administration Center for Drug Evaluation and Research: Guidance for industry: statistical approaches to establishing bioequivalence. Washington, DC: US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, 2001. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070244.pdf. Accessed May 11, 2010.

van Elteren PH. On the combination of independent two sample tests of Wilcoxon. Bulletin Intern Stat Inst. 1960;37:351-361.

Verma A. Epidemiology and clinical features of HIV-1-associated neuropathies. J Peripher Nerv Syst. 2001;6(1):8-13.

Wallace VC, Segerdahl AR, Blackbeard J, et al. Anxiety-like behavior is attenuated by gabapentin, morphine and diazepam in a rodent model of HIV anti-retroviral-associated neuropathic pain. Neurosci Lett. 2008:448(1):153-156.

Webster LR, Malan TP, Tuchman MM, Mollen MD, Tobias JK, Vanhove GF. A multicenter, randomized, double blind, controlled dose finding study of NGX 4010, a high concentration capsaicin patch, for the treatment of postherpetic neuralgia. J Pain. 2010;11(10):972-982.

Westlake WJ. Symmetrical confidence intervals for bioequivalence trials. Biometrics. 1976;32(4):741-744.

10. APPENDICES

Appendix A Capsaicin 8% Patch Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use QUTENZA safely and effectively. See full prescribing information for QUTENZA.

QUTENZA® (capsaicin) 8% patch
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------
- Qutenza is a TRPV1 channel agonist indicated for the management of neuropathic pain associated with postherpetic neuralgia (PHN). (0)

----------DOSAGE AND ADMINISTRATION----------
- Only physicians or health care professionals under the close supervision of a physician are to administer Qutenza. (2.1)
- Do not use Qutenza on broken skin. (2.1)
- Apply Qutenza to the most painful skin areas, using up to four patches. (2.2)
- Apply Qutenza for 60 minutes and repeat every 3 months or as warranted by the return of pain (not more frequently than every three months). (2.2)
- Use only nitrile (not latex) gloves when handling Qutenza and when cleaning treatment areas. (2.1)
- Before patch application, a physician must identify and mark the painful area, including areas of hypersensitivity and allodynia. (2.3)
- Apply a topical anesthetic before Qutenza application. (2.3)
- Apply Qutenza by placing on the skin while slowly removing the release liner from underneath. (2.3)
- Remove the Qutenza patches by gently and slowly rolling them inward. (2.3)
- After removal of Qutenza, apply Cleansing Gel for one minute and then remove it with a dry wipe. (2.3)
- Treat acute pain during and following the procedure with local cooling and/or analgesics. (5.4)
- Dispose of patches and other treatment materials immediately after use in accordance with local biomedical waste procedures. (2.1)
- The treated area may be sensitive for a few days to heat (e.g., hot showers/baths, direct sunlight, vigorous exercise). (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Qutenza patch contains 8% capsaicin (640 mcg/cm^2). Each patch contains a total of 179 mg of capsaicin. (0)

----------CONTRAINDICATIONS----------
- None

----------WARNINGS AND PRECAUTIONS----------
- Do not use near eyes or mucous membranes. (5.1)
- Inhalation of airborne capsaicin can result in coughing or sneezing. (5.2)
- If irritation of eyes or airway occurs, remove the affected individual from the vicinity of Qutenza and flush the mucous membranes or eyes with water. If skin not intended to be treated comes into contact with Qutenza, apply Cleansing Gel and then wipe off with dry gauze. (5.2, 5.3)
- Transient increases in blood pressure may occur in patients during and shortly after the Qutenza treatment. Monitor blood pressure during and following the treatment procedure. For those patients who require the use of opioids to treat pain during or following the procedure, their ability to perform potentially hazardous activities such as driving or operating machinery may be affected. (5.4, 5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 5% and greater than control) are application site erythema, application site pain, application site pruritus and application site papules. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact NeurogesX at 1-877-900-NGSX (6479) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: November 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Qutenza is indicated for the management of neuropathic pain associated with postherpetic neuralgia.

DOSAGE AND ADMINISTRATION

2.1 Special Precautions

- Only physicians or health care professionals under the close supervision of a physician are to administer Qutenza.
- Use only nitrile gloves when handling Qutenza, and when cleaning capsaicin residue from the skin. Do not use latex gloves as they do not provide adequate protection.
- Immediately after use, dispose of used and unused patches, Cleansing Gel and other treatment materials in accordance with the local biomedical waste procedures.
- Use Qutenza only on dry, intact (unbroken) skin.
- Apply the Qutenza patch within 2 hours of opening the pouch.

2.2 Dosing

The recommended dose of Qutenza is a single, 60-minute application of up to four patches.

Treatment with Qutenza may be repeated every three months or as warranted by the return of pain (not more frequently than every three months).

2.3 Instructions for Use

Prepare

Put on nitrile gloves. Inspect the pouch. Do not use if the pouch has been torn or damaged.

Identify

The treatment area (painful area including areas of hypersensitivity and allodynia) must be identified by a physician and marked on the skin.

If necessary, clip hair (do not shave) in and around the identified treatment area to promote patch adherence.

Qutenza can be cut to match the size and the shape of the treatment area.

Gently wash the treatment area with mild soap and water and dry thoroughly.

Anesthetize

Pre-treat with a topical anesthetic to reduce discomfort associated with the application of Qutenza.

Apply topical anesthetic to the entire treatment area and surrounding 1 to 2 cm, and keep the local anesthetic in place until the skin is anesthetized prior to the application of Qutenza patch.

Remove the topical anesthetic with a dry wipe. Gently wash the treatment area with mild soap and water and dry thoroughly.

Apply

Tear open the pouch along the three dashed lines, remove the Qutenza patch.

Inspect the Qutenza patch and identify the outer surface backing layer with the printing on one side and the capsaicin-containing adhesive on the other side. The adhesive side of the patch is covered by a clear, unprinted, diagonally-cut release liner.

Cut Qutenza before removing the protective release liner.

The diagonal cut in the release liner is to aid in its removal. Peel a small section of the release liner back, and place the adhesive side of the patch on the treatment area.

While you slowly peel back the release liner from under the patch with one hand, use your other hand to smooth the patch down on to the skin.

Once Qutenza is applied, leave in place for 60 minutes.

To ensure Qutenza maintains contact with the treatment area, a dressing, such as rolled gauze, may be used.

Instruct the patient not to touch the patch or treatment area.

Remove

Remove Qutenza patches by gently and slowly rolling them inward.

Cleanse

After removal of Qutenza, generously apply Cleansing Gel to the treatment area and leave on for at least one minute. Remove Cleansing Gel with a dry wipe and gently wash the area with mild soap and water and dry thoroughly.

Dispose of all treatment materials as described. [*see Dosage and Administration (2.1)*]

Inform the patient that the treated area may be sensitive for a few days to heat (e.g., hot showers/baths, direct sunlight, vigorous exercise).

DOSAGE FORMS AND STRENGTHS

Qutenza patch contains 8% capsaicin (640 mcg/cm^2). Each patch contains a total of 179 mg of capsaicin.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

5.1 Eye and Mucous Membrane Exposure

Do not apply Qutenza to the face or scalp to avoid risk of exposure to the eyes or mucous membranes.

5.2 Aerosolization of Capsaicin

Aerosolization of capsaicin can occur upon rapid removal of Qutenza patches. Therefore, remove Qutenza patches gently and slowly by rolling the adhesive side inward *[see Dosage and Administration (2.3)]*.

If irritation of eyes or airways occurs, remove the affected individual from the vicinity of Qutenza. Flush eyes and mucous membranes with cool water.

Inhalation of airborne capsaicin can result in coughing or sneezing. Provide supportive medical care if shortness of breath develops.

5.3 Unintended Skin Exposure

If skin not intended to be treated comes in contact with Qutenza, apply Cleansing Gel for one minute and wipe off with dry gauze. After the Cleansing Gel has been wiped off, wash the area with soap and water.

5.4 Application Associated Pain

Even following use of a local anesthetic prior to administration of Qutenza, patients may experience substantial procedural pain. Prepare to treat acute pain during and following the application procedure with local cooling (such as an ice pack) and/or appropriate analgesic medication, such as opioids. Opioids may affect the ability to perform potentially hazardous activities such as driving or operating machinery.

5.5 Increase in Blood Pressure

In clinical trials, increases in blood pressure occurred during or shortly after exposure to Qutenza. The changes averaged less than 10 mm Hg, although some patients had greater increases and these changes lasted for approximately two hours after patch removal. Increases in blood pressure were unrelated to the pretreatment blood pressure but were related to treatment-related increases in pain. Monitor blood pressure periodically during the treatment and provide adequate support for treatment related pain.

Patients with unstable or poorly controlled hypertension, a recent history of cardiovascular or cerebrovascular events may be at an increased risk of adverse cardiovascular effects. Consider these factors prior to initiating Qutenza treatment.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:
Application-Associated Pain [*see Warnings and Precautions (5.4)]*
Increase in Blood Pressure [*see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in clinical practice.

Across all controlled and uncontrolled trials, more than 1,600 patients have received Qutenza. A total of 394 patients received more than one treatment application and 274 patients were followed for 48 weeks or longer.

In controlled clinical studies, 98% of patients completed ≥ 90% of the intended patch application duration. Among patients treated with Qutenza, 1% discontinued prematurely due to an adverse event.

Controlled Clinical Studies

Common Adverse Reactions

Adverse reactions occurring in ≥ 5% of patients in the Qutenza group and at an incidence greater than in the control group were application site erythema, application site pain, application site pruritus and application site papules.

Table 1 summarizes all adverse reactions, regardless of causality, occurring in ≥ 1% of patients with postherpetic neuralgia in the Qutenza group for which the incidence was greater than in the control group. The majority of application site reactions were transient and self-limited. Transient increases in pain were commonly observed on the day of treatment in patients treated with Qutenza. Pain increases occurring during patch application usually began to resolve after patch removal. On average, pain scores returned to baseline by the end of the treatment day and then remained at or below baseline levels. A majority of Qutenza-treated patients in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate".

TABLE 1
Treatment-emergent adverse reaction incidence (%) in controlled trials in Postherpetic Neuralgia (Events in ³ 1% of Qutenza-treated patients and at least 1% greater in the Qutenza group than in the Control group)

Body System Preferred Term	Qutenza 60 minutes (N = 622) %	Control 60 minutes (N = 495) %
General Disorders and Administration Site Conditions		
Application Site Erythema	63	54
Body System Preferred Term	**Qutenza 60 minutes (N = 622) %**	**Control 60 minutes (N = 495) %**

Application Site Pain	42	21
Application Site Pruritus	6	4
Application Site Papules	6	3
Application Site Edema	4	1
Application Site Swelling	2	1
Application Site Dryness	2	1
Infections and Infestations		
Nasopharyngitis	4	2
Bronchitis	2	1
Sinusitis	3	1
Gastrointestinal Disorders		
Nausea	5	2
Vomiting	3	1
Skin and Subcutaneous Tissue Disorder		
Pruritus	2	< 1
Vascular Disorders		
Hypertension	2	1

Other Adverse Reactions Observed During the Clinical Studies of Qutenza

General Disorders and Administration Site Conditions: Application site urticaria, Application site paresthesia, Application site dermatitis, Application site hyperesthesia, Application site excoriation, Application site warmth, Application site anesthesia, Application site bruising, Application site inflammation, Application site exfoliation, Peripheral edema

Nervous System Disorders: Headache, Burning sensation, Peripheral sensory neuropathy, Dizziness, Dysgeusia, Hyperesthesia, Hypoesthesia

Respiratory, Thoracic and Mediastinal Disorders: Cough, Throat irritation

Skin and Subcutaneous Tissue Disorders: Abnormal skin odor

DRUG INTERACTIONS

No clinical drug interaction studies have been performed.

Data from *in vitro* cytochrome P450 inhibition and induction studies show that capsaicin does not inhibit or induce liver cytochrome P450 enzymes at concentrations which far exceed those measured in blood samples. Therefore, interactions with systemic medicinal products are unlikely.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category B

There are no adequate and well-controlled studies evaluating Qutenza in pregnant women.

There was no evidence of fetal teratogenicity in embryofetal developmental toxicological studies conducted in pregnant rats and rabbits in which Qutenza patches (rats) or liquid (rabbits) were applied once daily for a 3 hour duration during the period of fetal organogenesis up to doses corresponding to an 11-fold (rat, 32 mg capsaicin patch/day) and 37-fold (rabbit, 260 mg capsaicin/day) margin over the maximum recommended human dose [MRHD] based on a C_{max} exposure comparison.

In a peri- and post-natal reproduction toxicology study, pregnant female rats were treated with Qutenza patches at doses up to 32 mg capsaicin patch/rat/day applied once daily for a 3 hours duration during gestation and lactation (from gestation day 7 through day 28 postpartum). Analyses of milk samples on day 14 of the lactation period demonstrated measurable levels of capsaicin in the dam's milk at all dose levels. There were no effects on survival, growth, learning and memory tests (passive avoidance and water maze), sexual maturation, mating, pregnancy, and fetal development in the offspring of mothers treated with capsaicin up to 32 mg capsaicin patch/rat/day (corresponding to an 11-fold margin over the MRHD based on C_{max} exposure).

8.2 Labor and Delivery

The effects of Qutenza on labor and delivery are unknown.

8.3 Nursing Mothers

There are no adequate and well-controlled studies in nursing women. Studies in rat have demonstrated capsaicin is excreted into breast milk of this species. It is unknown whether capsaicin is excreted in human breast milk. Because Qutenza is administered as a single 60-minute application and capsaicin is rapidly cleared from the bloodstream [*see Clinical Pharmacology (12.3)*], mothers can reduce infant exposure by not breast-feeding after treatment on the day of treatment.

8.4 Pediatric Use

The safety and effectiveness of Qutenza in patients younger than 18 years of age have not been studied.

8.5 Geriatric Use

In controlled clinical studies of Qutenza in neuropathic pain associated with postherpetic neuralgia, 75% of patients were 65 years and older and 43% of patients were 75 years and older.

Safety and effectiveness were similar in geriatric patients and younger patients. No dose adjustments are required in geriatric patients.

10 OVERDOSAGE

There is no clinical experience with Qutenza overdose in humans.

There is no specific antidote for overdose with capsaicin. In case of suspected overdose, remove patches gently, apply Cleansing Gel for one minute, wipe off with dry gauze and gently wash the area with soap and water. Use supportive measures and treat symptoms as clinically warranted.

DESCRIPTION

Qutenza (capsaicin) 8% patch contains capsaicin in a localized dermal delivery system. The capsaicin in Qutenza is a synthetic equivalent of the naturally occurring compound found in chili peppers. Capsaicin is soluble in alcohol, acetone, and ethyl acetate and very slightly soluble in water.

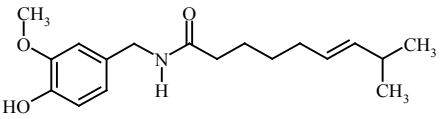
Qutenza is a single-use patch stored in a foil pouch. Each Qutenza patch is 14 cm x 20 cm (280 cm^2) and consists of a polyester backing film coated with a drug-containing silicone adhesive mixture, and covered with a removable polyester release liner.

The backing film is imprinted with "capsaicin 8%". Each Qutenza patch contains a total of 179 mg of capsaicin (8% in adhesive, 80 mg per gram of adhesive) or 640 micrograms (mcg) of capsaicin per square cm of patch.

The empirical formula is $C_{18}H_{27}NO_3$, with a molecular weight of 305.42. The chemical compound capsaicin [(E)-8-methyl-N-vanillyl-6-nonenamide] is an activating ligand for transient receptor potential vanilloid 1 receptor (TRPV1) and it has the following structure:

FIGURE 1:

Structural Formula of Capsaicin



The patch contains the following inactive ingredients: diethylene glycol monoethyl ether, dimethicone, ethyl cellulose, polyester film, silicone adhesive and white ink.

Qutenza is supplied with a Cleansing Gel which is used to remove residual capsaicin from the skin after treatment. Cleansing Gel consists of the following ingredients: butylated hydroxyanisole, carbomer copolymer, edetate disodium, polyethylene glycol, purified water, and sodium hydroxide.

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Capsaicin is an agonist for the transient receptor potential vanilloid 1 receptor (TRPV1), which is an ion channel-receptor complex expressed on nociceptive nerve fibers in the skin. Topical administration of capsaicin causes an initial enhanced stimulation of the TRPV1-expressing cutaneous nociceptors that may be associated with painful sensations. This is followed by pain relief thought to be mediated by a reduction in TRPV1-expressing nociceptive nerve endings [*see Clinical Pharmacology (12.2)*]. Over the course of several months, there may be a gradual re-emergence of painful neuropathy thought to be due to TRPV1 nerve fiber reinnervation of the treated area.

12.2 Pharmacodynamics

Two studies evaluated the pharmacodynamic effects of Qutenza on sensory function and epidermal nerve fiber (ENF) density in healthy volunteers. Consistent with the known pharmacodynamic effects of capsaicin on TRPV1-expressing nociceptive nerve endings, reduced ENF density and minor changes in cutaneous nociceptive function (heat detection and sharp sensation) were noted one week after exposure to Qutenza. ENF density reduction and sensory changes were fully reversible.

12.3 Pharmacokinetics

Pharmacokinetic data in humans showed transient, low (< 5 ng/mL) systemic exposure to capsaicin in about one third of PHN patients following 60-minute applications of Qutenza. The highest plasma concentration of capsaicin detected was 4.6 ng/mL and occurred immediately after Qutenza removal. Most quantifiable levels were observed at the time of Qutenza removal and were below the limit of quantitation 3 to 6 hours after Qutenza removal. No detectable levels of metabolites were observed in any subject.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Adequate carcinogenicity studies have not been conducted with Qutenza or capsaicin.

Mutagenesis

Capsaicin was not mutagenic in the Ames, mouse micronucleus and chromosomal aberration in human peripheral blood lymphocytes assays. As with other catechol-containing compounds (e.g., dopamine), capsaicin showed a weak mutagenic response in the mouse lymphoma assay.

Impairment of Fertility

A fertility and reproductive toxicology study was conducted in rats with exposure to Qutenza patches daily for 3 hours/day beginning 28 days before cohabitation, through cohabitation and continuing through the day before sacrifice (approximately 49 days of treatment). The results revealed a statistically significant reduction in the number and percent of motile sperm. Sperm motility obtained from the vas deferens was reduced in all capsaicin treatment groups (16, 24 and 32 mg capsaicin patch/rat/day). Though a "no effect" level was not determined, dose levels used in the study correspond to a 13- to 28-fold exposure margin over the mean C_{max} associated with the maximal human recommended dose. Sperm counts were reduced in the vas deferens or cauda epididymis in the 24 and 32 mg capsaicin patch/rat/day dose groups (79 and 69%, respectively) compared to the placebo patch treated control group; however, these reductions did not adversely affect fertility. As this animal model has a large excess of sperm generating capacity relative to the threshold necessary for fertilization, the lack of an effect on fertility in this species is of unknown significance for human risk assessment.

CLINICAL STUDIES

14.1 Postherpetic Neuralgia

The efficacy of Qutenza, was established in two 12-week, double-blind, randomized, dose-controlled, multicenter studies. These studies enrolled patients with postherpetic neuralgia (PHN) persisting for at least 6 months following healing of herpes zoster rash and a baseline score of 3-9 on an 11-point Numerical Pain Rating Scale (NPRS) ranging from 0 (no pain) to 10 (worst possible pain). Qutenza and a control patch were each applied as a single 60-minute application. The control used in these studies looked similar to Qutenza but contained a low concentration of the active ingredient, capsaicin (3.2 mcg/cm^2, 0.04% w/w) to retain blinding regarding the known application site reactions of capsaicin (such as burning and erythema). The baseline mean pain scores across the 2 studies was approximately 6.0. Patients who entered the study on stable doses of pain-control medications were required to keep dosing stable throughout the duration of the study. Approximately half of the patients were taking concomitant medications including anticonvulsants, non-SSRI antidepressants, or opioids for their PHN at study entry. Prior to study patch application a topical anesthetic was applied to the treatment area for 60 minutes. Patients were permitted to use local cooling and additional analgesic medications for treatment-related discomfort as needed through Day 5. Patients recorded their pain daily in a diary.

PHN Study 1: In this 12-week study, the Qutenza group demonstrated a greater reduction in pain compared to the Control group during the primary assessment at Week 8. The percent change in average pain from baseline to Week 8 was -18% (±2%) for the low-dose control and -29% (±2%) for Qutenza.

For various degrees of improvement in pain from baseline to study endpoint, Figure 2 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study through Week 12 or who showed no improvement at Week 12 were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study. The proportion of patients experiencing ≥ 30% reduction in pain intensity from baseline for each week through Week 12 is shown in Figure 3.

FIGURE 2:

Patients Achieving Various Percentages of Reduction in Pain Intensity at Week 12 – Study 1

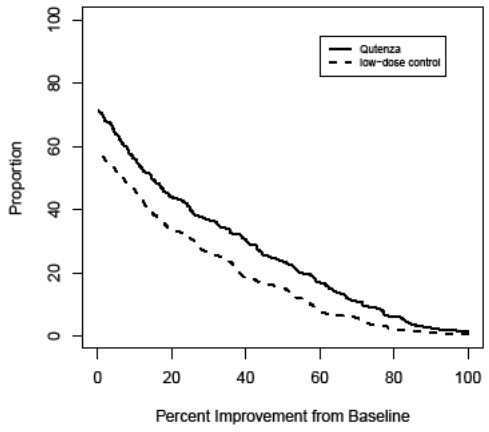
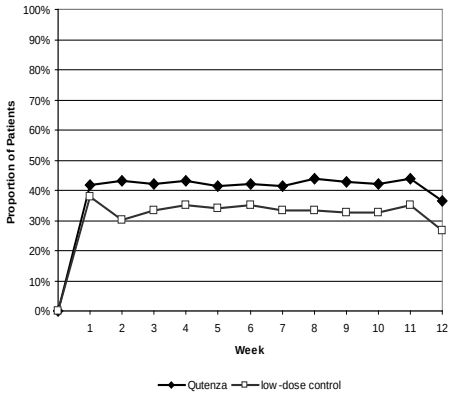


FIGURE 3:

Weekly Proportion of Patients Achieving ≥ 30% Pain Intensity Reduction – Study 1*



*The same patients may not have responded at each timepoint.

PHN Study 2: In this 12-week study the Qutenza group demonstrated a greater reduction in pain compared to the Control group during the primary assessment at Week 8. The percent change in average pain from baseline to Week 8 was -26% (±2%) for the low-dose control and -33% (±2%) for Qutenza.

For various degrees of improvement in pain from baseline to study endpoint, Figure 4 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study through Week 12 or who showed no improvement at Week 12 were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study. The proportion of patients achieving ≥ 30% reduction in pain intensity from baseline for each week through Week 12 is shown in Figure 5.

FIGURE 4:

Patients Achieving Various Percentages of Reduction in Pain Intensity at Week 12 – Study 2

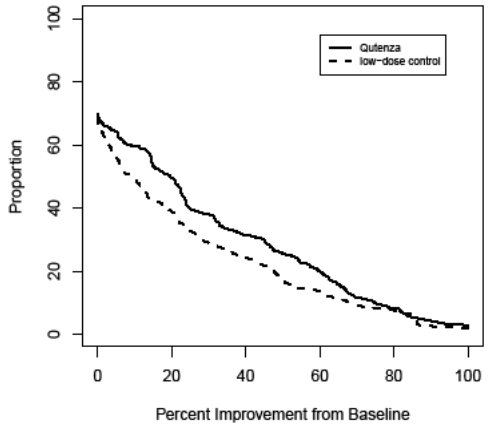
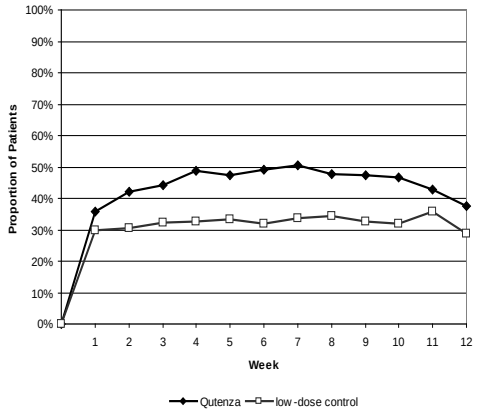


FIGURE 5:

Weekly Proportion of Patients Achieving ≥ 30% Pain Intensity Reduction – Study 2*



*The same patients may not have responded at each timepoint.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Qutenza (capsaicin) 8% patch is a single-use patch stored in a sealed pouch (NDC 49685-920-00).
Each individual patch is printed with "capsaicin 8%".
Cleansing Gel is provided in a 50 g tube.
Qutenza is available in the following presentations:
Carton of 1 patch and 50 g tube of Cleansing Gel
(NDC 49685-928-01).
Carton of 2 patches and 50 g tube of Cleansing Gel
(NDC 49685-928-02).

16.2 Storage

Store carton between 20° to 25°C (68° to 77°F). Excursions between 15°C and 30°C (59°F and 86°F) are allowed.
Keep the patch in the sealed pouch until immediately before use.

16.3 Handling and Disposal

Qutenza contains capsaicin capable of producing severe irritation of eyes, skin, respiratory tract and mucous membranes. Do not dispense Qutenza to patients for self-administration. It is critical that health care professionals who administer Qutenza have completely familiarized themselves with proper dosing, handling, and disposal procedures before handling Qutenza to avoid accidental or inadvertent capsaicin exposure to themselves or others [*see Dosage and Administration (2)*].

- Do not touch Qutenza, treatment areas, and all used supplies or other materials placed in contact with the treatment area without wearing nitrile gloves.
- Wear nitrile gloves at all times while handling Qutenza and cleaning treatment areas. Do NOT use latex gloves.
- Do not hold Qutenza near eyes or mucous membranes.
- Immediately after use, dispose of used and unused patches, patch clippings, unused Cleansing Gel and associated treatment supplies in accordance with local biomedical waste procedures.

PATIENT COUNSELING INFORMATION

- Inform patients that exposure of the skin to Qutenza may result in transient erythema and burning sensation. Instruct patients not to touch the patch and that if they accidentally touch the Qutenza patch it may burn and/or sting.
- Instruct patients that if irritation of eyes or airways occurs, or if any of the side effects become severe, to notify their doctor immediately.
- Inform patients that the treated area may be sensitive to heat (e.g., hot showers/bath, direct sunlight, vigorous exercise) for a few days following treatment.
- Inform patients that they may be given medication to treat acute pain during and after the Qutenza application procedure. Some of these medications, such as opioids, may affect the ability to perform potentially hazardous activities such as driving or operating machinery.
- Inform patients that as a result of treatment-related increases in pain, small transient increases in blood pressure may occur during and shortly after Qutenza treatment and that blood pressure will be monitored during the treatment procedure. Instruct patients to inform the physician if they have experienced any recent cardiovascular event
- Instruct patients to notify their physician if they are pregnant or breast feeding.

Manufactured for NeurogesX, Inc., San Mateo, CA 94404, USA
by Lohmann Therapie-Systeme AG (LTS), Andernach, Germany

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Appendix B Studies Evaluating Interventions for HIV-Associated Peripharal Neuropathy

Intervention	Design		Primary Endpoint	Significantly Better? (Results)	Reference
Acupuncture versus amitriptyline	DB, R, PC	250	Change in pain score at 6 and 14 weeks	**NO** (For both acupuncture and amitriptyline, changes in pain score were not significantly different between the active and placebo groups.)	Shaly, 1998
Cannabis	R, PC	55	Change in rating of chronic pain by VAS and percentage of patients achieving >30% reduction in pain intensity at Day 5	**YES** (Smoked cannabis reduced daily pain by 34% versus 17% with placebo [P = 0.03]; 52% versus 24% of subjects in the respective groups reported > 30% reduction in pain [P = 0.04].)	Abrams, 2007
Cannabis	R, PC, CO	34	Change in pain intensity assessed by the 21-point Descriptor Differential Scale (DDS) at Day 5 of each treatment week	**YES** (Among the completers [n=28], pain relief was greater with cannabis than placebo [median difference in DDS pain intensity change, 3.3 points, effect size=0.60; P=0.016].)	Ellis, 2009
Gabapentin	DB, R, PC	26	Change in VAS (0-100) from Screening week to 4th treatment week	**NO** (Median change in VAS from baseline to week 4 was greater with gabapentin [-44.1%] than with placebo [-29.8%].)	Hahn, 2004
Lamotrigine	DB, R, PC	227	Change in Gracely Pain Scale score at end of 4-week maintenance phase	**NO** (No difference between lamotrigine and placebo was observed in mean change from baseline in average pain score [Gracely Pain Scale] at week 4.)	Simpson, 2003
5% Lidocaine Gel	DB, R, PC, CO	64	Change in pain score (Gracely Pain Scale) during the second week of each 2-week treatment period	**NO** (There was no difference between lidocaine gel and placebo based on average pain score during the second week of each CO phase.)	Estanislao, 2004
Memantine	R, PC	45	Change in mean pain score (10-point rating scale) and change in mean paresthesia score (10-point rating scale) at Week 16	**NO** (No trend toward clinical benefit was observed with memantine.)	Schifitto, 2006
Mexiletine	DB, R, PC, CO	19	Daily pain response by VAS	**NO** (There was no statistically significant	Kemper, 1998

				difference between the mean daily pain scores for patients receiving mexiletine versus placebo, irrespective of the order in which the agents were received.)	
Mexiletine or Amitriptyline	DB, R, PC	145	Change in pain intensity at final visit (Week 10)	**NO** (Improvement [mean ± SD] in amitriptyline group [0.31±0.31 units] and mexiletine group [0.23±0.41 units] was not significantly different from placebo [0.20±0.30].)	Kieburtz, 1998
Peptide T	DB, R, PC	81	Change in the modified Gracely Pain Scale score at Week 12	**NO** (There was no difference between Peptide T and placebo based on change in pain score at Week 12 [-0.24 versus -0.39; P = 0.32].)	Simpson, 1996
Pregabalin	DB, R, PC	302	Change in mean Numeric Pain Rating Scale (NPRS) score (11-point rating scale) at Week 12	**NO** (At endpoint, reduction in NPRS score from baseline was similar for the pregabalin and placebo groups [-2.88 versus -2.63, P = 0.3941].)	Simpson, 2010
rhNGF	DB, R, PC	270	Change in self-reported neuropathic pain intensity (Gracely Pain Scale)	**YES** (Both doses of rhNGF [0.1 and 0.3 µg/kg] produced significant improvements in average and maximum daily pain compared with placebo.)	McArthur, 2000
Low-dose capsaicin (0.075%)	DB, R, PC	26	Change in self-reporting peripheral neuropathic pain during the 4-week trial	**NO** (No statistically significant differences between capsaicin and vehicle groups for current pain, worst pain, pain relief, sensory perception, quality of life, mood or function and any time during study; capsaicin subjects reported higher current pain scores at end of 1 week.)	Paice, 2000

CO = crossover, DB = double-blind, PC = placebo-controlled, N = number of patients, R = randomized, rhNGF = recombinant human nerve growth factor, VAS = Visual Analogue Scale.

Appendix C Capsaicin 8% Patch Study Information

Capsaicin 8% Patch study information is summarized in Table 30.

Table 30 Description of Capsaicin 8% Patch Studies in HIV-PN

Study ID Number of Centers Duration	Study Design	Study Drug & Low-dose Control Dose	Study Objective	Number of Subjects by Arm Entered/ Completed	Sex M/F Mean[1] Age (Range)	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint	Safety Endpoints
Controlled Studies – HIV-PN								
C107 32 centers 12 weeks + 40 wks	Phase 3, 12-week, randomized, double-blind, controlled, multicenter study followed by a 40-week open-label extension phase	Capsaicin 8% Patch (capsaicin patch, 640 µg/cm^2, 8% w/w): single application of 30, 60, or 90 minutes. Low-dose Control (capsaicin patch, 3.2 µg/cm^2, 0.04% w/w): single application of 30, 60, or 90 minutes. Open-label Capsaicin 8% Patch: single application of 60 minutes, could be repeated up to 3 times (separated by a minimum of 12 weeks) within 40 weeks	To assess the efficacy, safety, and tolerability of Capsaicin 8% Patch at 3 different dose levels	Double-blind Capsaicin 8% Patch[2] 30 min: 72/65 60 min: 78/70 90 min: 75/66 Double-blind Low-dose Control[b] 30 min: 27/21 60 min: 26/24 90 min: 29/26 Open-label Extension 272/188: 81/90/55/46 received 0, 1, 2, and 3 retreatments, respectively	Double-blind Capsaicin 8% Patch 30 min: 63 M/9 F 47.2 ± 8.59 (29-66) 60 min: 73 M/5 F 48.3 ± 7.82 (33-74) 90 min: 71 M/4 F 46.9 ± 8.31 (30-69) Low-dose Control 30 min: 26 M/1 F 47.7 ± 6.88 (33-62) 60 min: 25 M/1 F 50.7 ± 8.02 (38-70) 90 min: 28 M/1 F 47.1 ± 7.73 (36-65)	Double-Blind Phase: Moderate to severe neuropathic pain in both feet for ≥2 months prior to Screening secondary to HIV-PN (from HIV and/or neurotoxic antiretroviral drug exposure). Screening Pain Sum Score of 12 to 36 over 4 consecutive days (equivalent to a mean score of 3-9). If taking chronic pain medications, on a stable regimen for ≥21 days prior to Treatment Visit. Open-Label Phase: Re-treatments were optional and based on the persistence (< 25% improved from pre-randomization Baseline) or reemergence (> 20% increased from double-blind Weeks 2-3 average) of pain.	Double-Blind Phase: Percent change from Baseline in the "average pain for the past 24 hours" NPRS score during Weeks 2–12.	• AE monitoring • Clinical laboratory tests • Evaluation of vital signs and physical examinations • HIV disease status • Duration of patch application • Dermal irritation • Targeted neurological/sensory assessments • Heat pain, cooling, and vibration perception thresholds QST • Nerve conduction evaluations • Change in "pain now" NPRS scores in evening of treatment day • Number of subjects requiring medication for treatment-related discomfort during first 5 days after patch application

Table 30 Description of Capsaicin 8% Patch Studies

Study ID Number of Centers Duration	Study Design	Study Drug & Low-dose Control Dose	Study Objective	Number of Subjects by Arm Entered/ Completed	Sex M/F Mean[1] Age (Range)	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint	Safety Endpoints
Controlled Studies – HIV-PN (Continued)								
C119 78 centers 12 weeks	Phase 3, randomized, double-blind, controlled, multicenter study	Capsaicin 8% Patch (capsaicin patch, 640 µg/cm^2, 8% w/w): single application of 30 or 60 minutes Low-dose Control (capsaicin patch, 3.2 µg/cm^2, 0.04% w/w): single application of 30 or 60 minutes	To assess the efficacy, safety and tolerability over 12 weeks of Capsaicin 8% Patch applied for 30 or 60 minutes for the treatment of painful HIV-PN	Double-blind Capsaicin 8% Patch 30 min: 167/156 60 min: 165/153 Double-blind Low-dose Control 30 min: 73/71 60 min: 89/81	Double-blind Capsaicin 8% Patch 30 min: 142 M/ 25 F 50.5 ± 8.34 (26-72) 60 min: 148 M/ 17 F 49.0 ± 8.52 (22-69) Double-blind Low-dose Control 30 min: 63 M/ 9 F 49.3 ± 7.78 (31-69) 60 min: 79 M/ 11 F 50.1 ± 9.33 (29-74)	Moderate to severe neuropathic pain (average Baseline NPRS scores of 3 to 9) in both feet for at least 2 months prior to Screening secondary to HIV-PN resulting from HIV disease and/or neurotoxic dideoxy-nucleoside analogue antiretroviral drug exposure. If on neurotoxic antiretrovirals, currently on stable dose(s) for at least for at least 2 months prior to Screening. If taking chronic pain medications, must be on a stable regimen for at least 21 days prior to treatment visit.	Percent change from Baseline in the "average pain for the past 24 hours" NPRS score during Weeks 2–12.	• AE monitoring • Clinical laboratory tests • Dermal irritation • Duration of patch application • Change in "pain now" NPRS scores in the evening on the day of treatment • Number of subjects reporting a pain increase (NPRS) during the first 48 hours after patch application • Number of subjects requiring medication for treatment-related discomfort during the first 5 days after patch application

Table 30 Description of Capsaicin 8% Patch Studies

Study ID Number of Centers Duration	Study Design	Study Drug & Low-dose Control Dose	Study Objective	Number of Subjects by Arm Entered/ Completed	Sex M/F Mean[1] Age (Range)	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint	Safety Endpoints
Controlled Studies – HIV-PN (Continued)								
C112[3] 2 centers 12 weeks	Phase 3, randomized, double-blind, controlled, multicenter study	Capsaicin 8% Patch (capsaicin patch, 640 µg/cm^2, 8% w/w): single application of 60 minutes Low-dose Control (capsaicin patch, 3.2 µg/cm^2, 0.04% w/w): single application of 60 minutes	1) To assess the efficacy over 12 weeks 2) To assess the tolerability and safety of Capsaicin 8% Patch versus low-dose Control patch	5/0[3]	5 M/ 0 F 49.0 ± 4.00 (44-55)	Painful HIV-PN with neuropathic pain secondary to HIV-PN and/or antiretroviral toxic neuropathy in both feet for at least 2 months prior to Screening. If taking chronic pain medications, must be on a stable regimen for at least 21 days prior to Treatment Visit. If on neurotoxic antiretrovirals, currently on stable dose(s) for at least 8 weeks prior to the Screening Visit, without a foreseeable need to change doses or medications for the duration of study.	Percent change from Baseline in the "average pain for the past 24 hours" NPRS score during Weeks 2–12.	• AE monitoring • Clinical laboratory tests • Evaluation of vital signs and physical examinations • Dermal irritation • Duration of patch application • Targeted neurological/sensory assessments • Number of subjects reporting a pain increase (NPRS) during the first 48 hours after patch application • Number of subjects requiring medication for treatment-related discomfort during the first 5 days after patch application

Table 30 Description of Capsaicin 8% Patch Studies

Study ID Number of Centers Duration	Study Design	Study Drug & Low-dose Control Dose	Study Objective	Number of Subjects by Arm Entered/ Completed	Sex M/F Mean[1] Age (Range)	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint	Safety Endpoints
Open-Label Studies – HIV-PN								
C109 3 centers 12 weeks	Phase 2, multicenter, open-label study	Capsaicin 8% Patch (capsaicin patch, 640 µg/cm^2, 8% w/w): single application of 60 minutes	To obtain preliminary information on the feasibility, tolerability, efficacy, and safety of Capsaicin 8% Patch	12/11	9 M/ 3 F 44.0 ± 6.93 (32-52)	Moderate to severe neuropathic pain secondary to HIV-PN in both feet. Screening Pain Sum Score of 12 to 36 (equivalent to mean Baseline score of 3-9). If taking chronic pain medications must have been on a stable regimen for at least 7 days prior to the Treatment Visit. If on neurotoxic antiretroviral, on stable dose(s) for at least 8 weeks prior to the Screening Visit, without a foreseeable need to change doses or medications for the duration of study.	Percent change from Baseline in the "average pain for the past 24 hours" NPRS score during Weeks 2–12.	• AE monitoring • Clinical laboratory tests • Vital signs and physical examinations • Duration of patch application • Dermal irritation • Targeted neurological/sensory assessments • Number of subjects requiring medication for treatment-related discomfort during the first 5 days after patch application

Table 30 Description of Capsaicin 8% Patch Studies

Study ID Number of Centers Duration	Study Design	Study Drug & Low-dose Control Dose	Study Objective	Number of Subjects by Arm Entered/ Completed	Sex M/F Mean[1] Age (Range)	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint	Safety Endpoints
Open-Label Studies – HIV-PN								
C111 17 centers 12 weeks	Phase 2, randomized, open-label, multicenter study	Capsaicin 8% Patch (capsaicin patch, 640 µg/cm^2, 8% w/w): single application of 60 or 90 minutes Lidocaine 4% local skin anesthetic- LMX 4®, Topicaine®, or Betacaine®: single application of 60 minutes prior to Capsaicin 8% Patch treatment	To assess the tolerability of Capsaicin 8% Patch following 1 of 3 lidocaine 4% local skin anesthetic creams	LMX4 60 min: 19/16 90 min: 20/17 Topicaine 60 min: 19/17 90 min: 19/17 Betacaine 60 min: 20/17 90 min: 20/19 PDN: n = 91: 47 for 90 min and 44 for 60 min PHN: n = 25: 12 for 90 min and 13 for 60 min, HIV-PN: n = 1: 60 min	LMX4 60 min: 8 M/ 11 F 61.1 ± 11.84 (41-82) 90 min: 14 M/ 6 F 64.1 ± 13.47 (41-89) Topicaine 60 min: 13 M/ 6 F 60.3 ± 12.11 (37-84) 90 min: 10 M/ 9 F 63.8 ± 11.18 (43-79) Betacaine 60 min: 9 M/ 11 F 56.5 ± 11.75 (37-72) 90 min: 14 M/ 6 F 59.8 ± 11.17 (41-81)	Screening Pain Sum Score of 12 to 32 over 4 consecutive days (equivalent to a mean score of 3-8). Documented diagnosis of PDN, PHN or HIV-PN for at least 3 months prior to the Screening Visit. If taking chronic pain medications, must be on a stable regimen for at least 21 days prior to Treatment Visit. If on neurotoxic antiretrovirals, currently on stable dose(s) for at least 8 weeks prior to the Screening Visit, without a foreseeable need to change doses or medications for the duration of study.	Percent change from Baseline in the "average pain for the past 24 hours" NPRS score during Weeks 2–12.	• AE monitoring • Clinical laboratory tests • Evaluation of vital signs and physical examinations • Dermal irritation • Targeted neurological/sensory assessments • Duration of patch application • Number of subjects reporting a pain increase (NPRS) during the first 48 hours after patch application • Number of subjects requiring medication for treatment-related discomfort during the first 5 days after patch application

Table 30 Description of Capsaicin 8% Patch Studies

Study ID Number of Centers Duration	Study Design	Study Drug & Low-dose Control Dose	Study Objective	Number of Subjects by Arm Entered/ Completed	Sex M/F Mean[1] Age (Range)	Diagnosis Inclusion Criteria	Safety Endpoints
Repeat-Treatment Study							
C118 19 centers 48 weeks	Phase 2, randomized, open-label, multicenter study	Capsaicin 8% Patch (capsaicin patch, 640 µg/cm^2, 8% w/w): up to 4 applications of 60 minutes (PHN and HIV-PN subjects) or 90 minutes (HIV-PN subjects) at least 12 weeks apart	To assess the safety and efficacy of repeated application of Capsaicin 8% Patch over 1 year for the treatment of HIV-PN and PHN.	106/79 26/11/31/38 received a total of 1, 2, 3 and 4 treatments. 25 subjects (24 with PHN and 1 with HIV-PN) had not received a previous Capsaicin 8% Patch treatment.	69 M/ 37 F 60.6 ± 12.93 (36-86)	Successful completion of participation in a past study of Capsaicin 8% Patch. Moderate to severe neuropathic pain secondary to HIV-PN or PHN, with average pain levels deemed appropriate for further treatment with Capsaicin 8% Patch as judged by the Investigator. If taking chronic pain medications, must be on a stable regimen for at least 14 days prior to treatment visit.	• AE monitoring • Clinical laboratory tests • Evaluation of vital signs and physical examinations • Duration of patch application • Change in "pain now" NPRS scores on the day of treatment • Dermal irritation • Targeted neurological/sensory assessments • Proportion of subjects requiring medication for treatment-related discomfort during the first 5 days after patch application

AE=adverse event; ECG=electrocardiogram; F=Female; HIV-PN = human immunodeficiency virus-associated peripheral neuropathy; M=Male; NPRS=Numeric Pain Rating Scale; PRN=as needed; QST=Quantitative Sensory Testing.

NOTES:

1. Data reported as mean age (years) ± standard deviation.
2. The number of subjects completing the study represents subjects completing the double-blind phase.
3. Study C112 was terminated prematurely following unblinding of Study C107 demonstrating statistical significance in HIV-PN for the 30- and 90-minute doses. Only 5 subjects were enrolled in the study before it was terminated.

Appendix D Clinical Assessments for Studies C107 and C119

Numeric Pain Rating Scale (Pain Now)

Subjects will be instructed to provide pain ratings relative only to the areas of pain undergoing investigational treatment.

Form A – Day of Treatment Numeric Pain Rating Scale

Please circle the one number that best describes how much pain you have right now:

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

Form B –Numeric Pain Rating Scale

Please circle the one number that best describes your pain on the average in the last 24 hours:

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

Briefing Pain Inventory (BPI)

A modified version of the BPI (Short Form) was used that included Questions 3-6 on pain levels and Question 9 (A-G) regarding interference of pain on the subject's ability to function. Subjects rated their pain on a scale of 0 (no pain) to 10 (worst possible pain) in response to these pain-related categories:

1. Pain at its worst in the last 24 hours.
2. Pain at its least in the last 24 hours.
3. Pain on average in the last 24 hours.
4. Pain right now.
5. How pain has interfered with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life in the last 24 hours.

Brief Pain Inventory-Short Form (BPI)

1. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.
0 1 2 3 4 5 6 7 8 9 10 No Pain ... Worst possible pain
2. Please rate your pain by circling the one number that best describes your pain on the least in the last 24 hours.
0 1 2 3 4 5 6 7 8 9 10 No Pain ... Worst possible pain
3. Please rate your pain by circling the one number that best describes your pain on the average in the last 24 hours.
0 1 2 3 4 5 6 7 8 9 10

No Pain	Worst possible pain

4. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst possible pain

5. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Brief Pain Inventory-Short Form (BPI) (continued)

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10

Does not interfere	Completely interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Adapted from: Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain. 1983 Oct;17(2):197-210.

Global Impression of Change Scales

Patient Global Impression of Change (PGIC)

Please mark one response below to indicate **how you feel now**, compared to how you felt before receiving treatment in this study.

☐ I feel very much improved (3)

☐ I feel much improved (2)

☐ I feel slightly improved (1)

☐ I feel no change (0)

☐ I feel slightly worse (-1)

☐ I feel much worse (-2)

☐ I feel very much worse (-3)

Clinical Global Impression Of Change (CGIC)

Please mark one response below to indicate **how the subject appears to you now**, compared to how they appeared to you before receiving treatment in this study.

☐ Subject very much improved (3)

☐ Subject much improved (2)

☐ Subject slightly improved (1)

☐ See no change (0)

☐ Subject slightly worse (-1)

☐ Subject much worse (-2)

☐ Subject very much worse (-3)

Self-Assessment of Treatment (SAT)

Self-Assessment of Treatment (SAT) at Week 12 were summarized within each group and compared between the active and the low-dose Control groups.

Subjects were asked to assess capsaicin patch treatment by answering the following

5 questions:

1. How do you assess your pain level after treatment in this study?
2. How do you assess your activity level after treatment in this study?
3. How has your quality of life changed after treatment in this study?
4. Would you undergo this treatment again?
5. How do you compare the treatment you received in this study to previous medication
   or therapies for your pain?

For each of these questions except Question 4, the subject checked a box on a 5-point scale, with the middle option indicating a neutral response and the lower and higher options indicating a negative or positive response, respectively. For Question 4, the subject had 3 options (No, absolutely not; Unsure; Yes, definitely).

Self-Assessment of Treatment (SAT)

Please mark one response for each question below.

1. How do you assess your pain level after treatment in this study?

☐ I feel my pain is much worse (-2)

☐ I feel my pain is somewhat worse (-1)

☐ I feel my pain is no better and no worse (0)

☐ I feel my pain is somewhat better (1)

☐ I feel my pain is much better (2)

2. How do you assess your activity level after treatment in this study?

☐ I feel much less active (-2)

☐ I feel somewhat less active (-1)

☐ I feel no more and no less active (0)

☐ I feel somewhat more active (1)

☐ I feel much more active (2)

3. How has your quality of life changed after treatment in this study?

☐ I feel my quality of life is much worse (-2)

☐ I feel my quality of life is somewhat worse (-1)

☐ I feel my quality of life is no better and no worse (0)

☐ I feel my quality of life is somewhat better (1)

☐ I feel my quality of life is much better (2)

4. Would you undergo this treatment again?

☐ No, absolutely not (-1)

☐ Unsure (0)

☐ Yes, definitely (1)

5. How do you compare the treatment you received in this study to previous medication or therapies for your pain?

☐ Very much prefer my previous treatments to this treatment (-2)

☐ Somewhat prefer my previous treatments (-1)

☐ No preference (0)

☐ Somewhat prefer this treatment to my previous treatments (1)

☐ Very much prefer this treatment to my previous treatments (2)

Short-Form McGill Pain Questionnaire (SF-MPQ)

The words below describe different kinds of pain. Place a check mark (ü) in the column that represents the degree to which you feel each type of pain.

	NONE	MILD	MODERATE	SEVERE
THROBBING	0)____	1)____	2)____	3)____
SHOOTING	0)____	1)____	2)____	3)____
STABBING	0)____	1)____	2)____	3)____
SHARP	0)____	1)____	2)____	3)____
CRAMPING	0)____	1)____	2)____	3)____
GNAWING	0)____	1)____	2)____	3)____
HOT-BURNING	0)____	1)____	2)____	3)____
ACHING	0)____	1)____	2)____	3)____
HEAVY	0)____	1)____	2)____	3)____
TENDER	0)____	1)____	2)____	3)____
SPLITTING	0)____	1)____	2)____	3)____
TIRING-EXHAUSTING	0)____	1)____	2)____	3)____
SICKENING	0)____	1)____	2)____	3)____
FEARFUL	0)____	1)____	2)____	3)____
PUNISHING-CRUEL	0)____	1)____	2)____	3)____

PPI (Present Pain Intensity) - Place a check mark (ü) in the appropriate row.

0	NO PAIN	____
1	MILD	____
2	DISCOMFORTING	____
3	DISTRESSING	____
4	HORRIBLE	____
5	EXCRUCIATING	____

Adapted from: Melzack R. The short-form McGill Pain Questionnaire. Pain. 1987 Aug;30(2):191-7.

Dermal Assessment Scoring

Dermal Assessment Scale

0 = no evidence of irritation

1 = minimal erythema, barely perceptible

2 = definite erythema, readily visible; minimal edema or minimal papular response

3 = erythema and papules

4 = definite edema

5 = erythema, edema, and papules

6 = vesicular eruption

7 = strong reaction spreading beyond test site

Appendix E Statistical Methods

Analyses of Primary Endpoint

Additional analyses of the primary endpoint were performed for the pivotal Study C107 and Study C119 to examine the robustness of the efficacy findings.

Study C107: Alternative to the Primary Analysis

In addition to the prespecified hierarchical primary analysis which assumes linear monotonic dose response, the following closed-test procedure [Marcus 1976], which evaluates each treatment arm independently and does not assume a linear monotonic dose response, was performed to analyze the primary endpoint with the following sort order:

- H_{01}: μ of 30 minute application = μ of 60 minute application = μ of 90 minute application = μ of total control group.
- H_{02}:
  - $H_{02\text{-}1}$: μ of 30-minute application = μ of 60-minute application = μ of total control group;
  - $H_{02\text{-}2}$: μ of 30-minute application = μ of 90-minute application = μ of total control group;
  - $H_{02\text{-}3}$: μ of 60-minute application = μ of 90-minute application = μ of total control group.
- H_{03}:
  - $H_{03\text{-}1}$: μ of 30-minute application = μ of total control group;
  - $H_{03\text{-}2}$: μ of 60-minute application = μ of total control group;
  - $H_{03\text{-}3}$: μ of 90-minute application = μ of total control group

This test procedure first investigates, at a significance level of 0.05, whether H_{01} can be rejected. In the case where H_{01} can be rejected, each of the H_{02} hypotheses are tested at a significance level of 0.05. Those H_{02} hypotheses that are rejected are tested as relevant H_{03} hypotheses at a significance level of 0.05.

Although like the prespecified primary analysis, this method is hierarchical; it does not assume a linear monotonic relationship between application duration and response and still controls the study -wide type I error equals to 5%. Besides the closed testing procedure, two other methods

of multiple comparison methods were applied to the primary endpoint. These are Bonferroni and Hochberg multiple testing procedures.

Study C119: Alternative to the Primary Analysis

To compare across both Phase 3 studies, the ANCOVA model used in pivotal Study C107 was applied to Study C119 and differences between groups were compared by a gender-stratified ANCOVA model with Baseline pain score, pre-LMX4 pain score, and percent change in pain score after LMX4 treatment as covariates. This approach was selected as it used the prespecified covariates from the pivotal Study C107 to enhance the comparability of results between the two studies.

Study C107 and Study C119: Alternative to the Primary Analysis

Dworkin and colleagues [Dworkin 2011] have recommended that assumptions underlying the use of parametric models should be assessed and study conclusions should be examined to determine whether they depend on the method of analysis. In the presence of non-normality, the assumptions underlying parametric analyses such as the prespecified primary ANCOVA analysis, consisting of normality of error terms, equality of error variances for different treatments, and/or equality of slopes for the different treatment regression lines, will no longer be valid. To address this issue, a Shapiro–Wilk test [Shapiro 1965] to evaluate normality was performed on the residuals of the primary endpoint analyses and the following two nonparametric analyses, which are appropriate for situations in which the normality assumptions are not satisfied, were subsequently conducted:

1. A rank analysis of covariance [Quade 1967], which can be combined with the randomization model framework of extended Cochran Mantel Haenszel statistics to carry out nonparametric comparisons between treatment groups, after adjusting for the effects of one or more covariates. The methodology has been described by Koch et al. [Koch 1982; Koch 1990] and can be implemented using the SAS System [Stokes 1995].

A stratified Wilcoxon [van Elteren 1960] test. This test is stratified by gender and patch duration for comparison between the total groups and by gender only for comparison of the individual application time groups with the total (Study C107) groups and does not include adjusting for the effects of one or more covariates.